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British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

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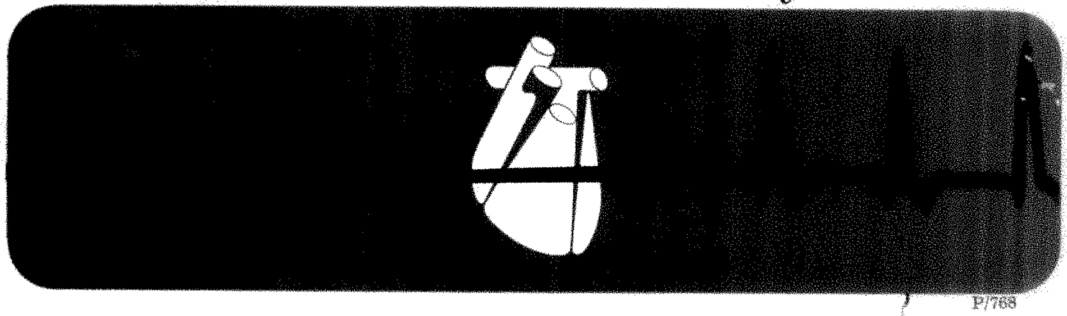

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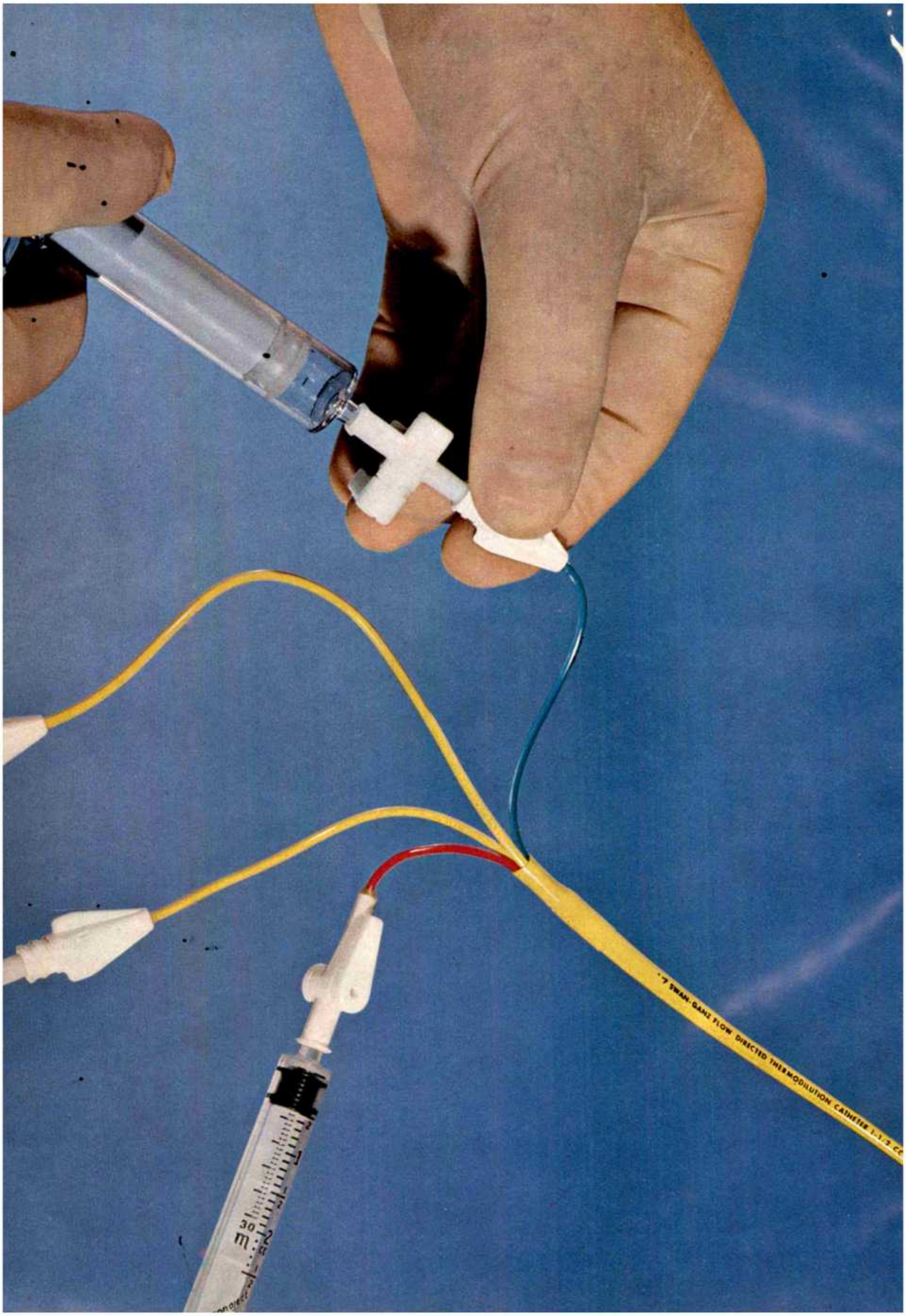
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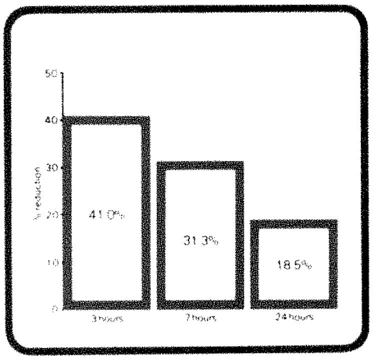

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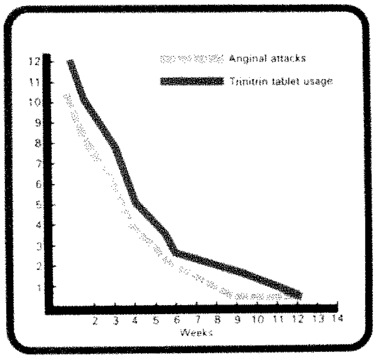

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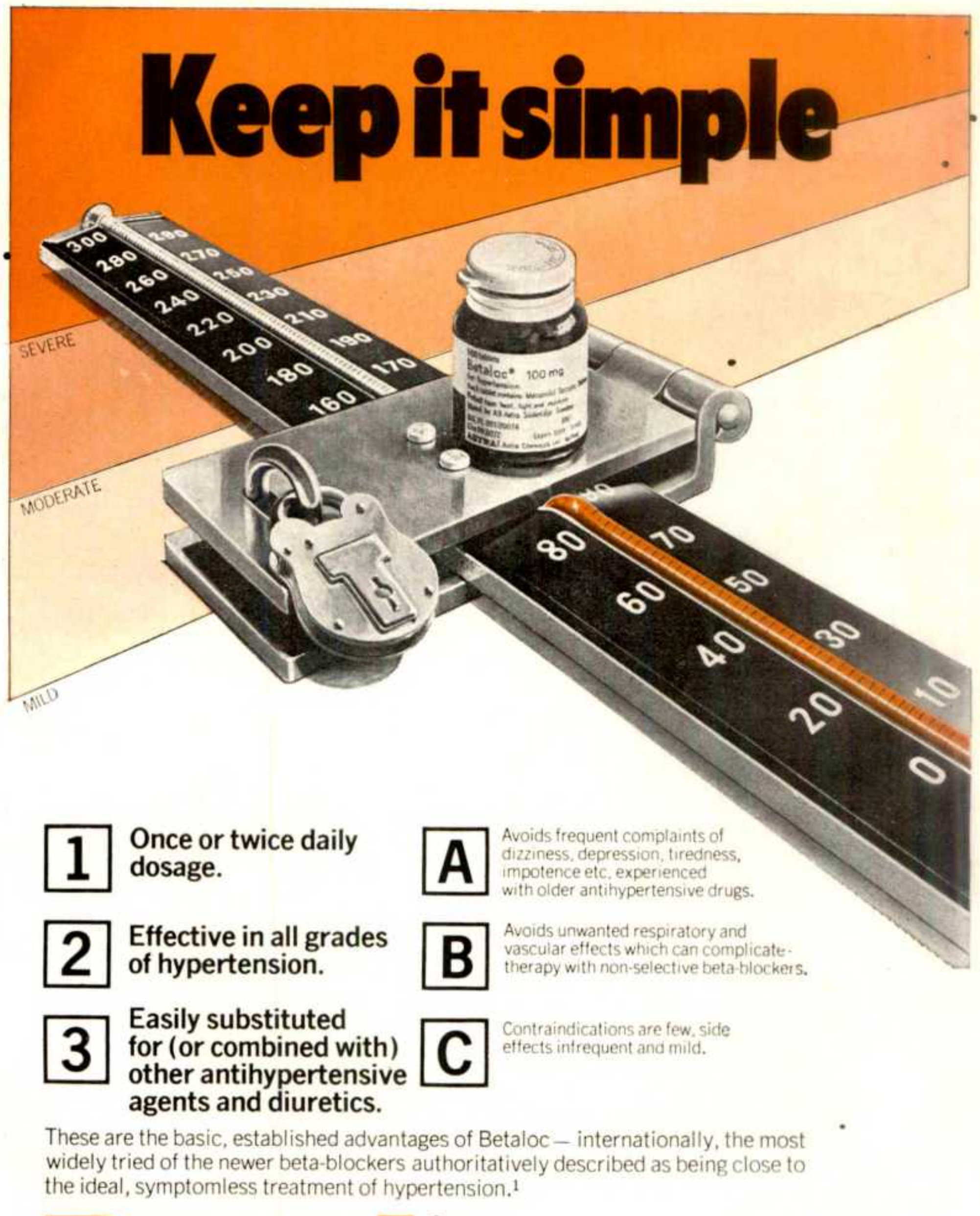

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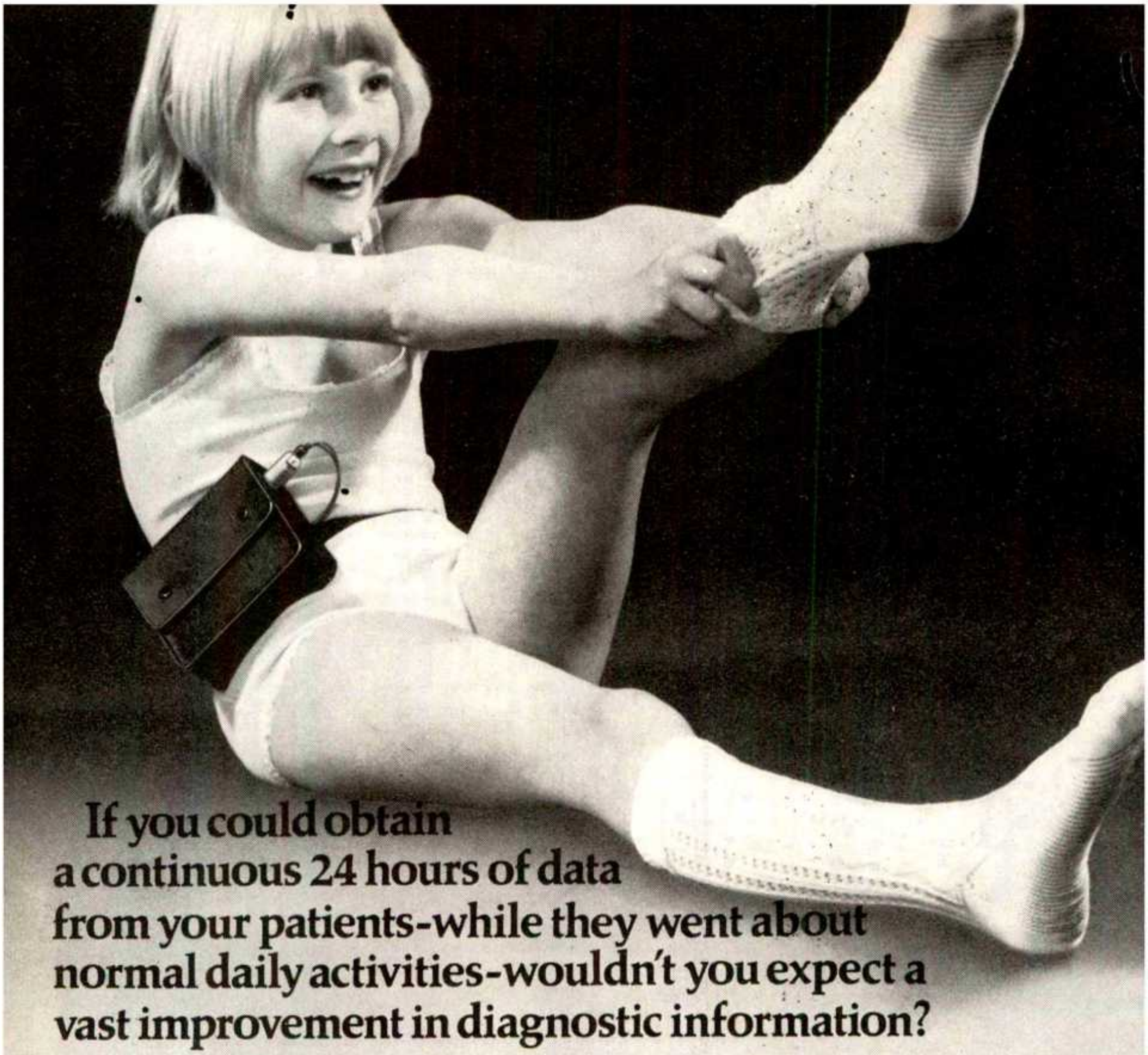

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Relation between apex cardiogram and changes in left ventricular pressure and dimension

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The relation between the apex cardiogram and changes in left ventricular pressure measured by micromanometer, and dimension measured by echocardiography, was studied in 12 normal subjects and 64 patients with heart disease. In 12 patients, the apex cardiogram was delayed with respect to simultaneous left ventricular pressure by 17±18 ms during the upstroke and 28±16 ms during the downstroke. In the normal subjects, changes in left ventricular dimension during the upstroke and downstroke of the apex cardiogram were small, amounting to 6±5 and 21±7 per cent total excursion, respectively. In 10 patients with mitral regurgitation, there was significant inward wall movement during the upstroke and in 10 patients with aortic regurgitation, significant outward movement during the downstroke, both reflecting valvular regurgitation. In 20 patients with ischaemic heart disease and segmental abnormalities on left ventricular angiography, apex cardiogram-echo dimension relations were abnormal in all, because of inward or outward wall movement during the upstroke, increased outward movement before the 'O' point, or abnormal inward movement during the downstroke. These disturbances were displayed by constructing apex cardiogram-echo dimension loops, which appear to be a sensitive means of detecting incoordinate left ventricular contraction, analogous to those between pressure and dimension.

A limitation in the use of M-mode echocardiography in studying left ventricular function is that wall movement is recorded from only a localized region of cavity, so that it is not possible to tell whether a change in dimension results from filling or ejection on the one hand, or from an isovolumic shape change on the other. The value of the technique would, therefore, be increased if information were simultaneously available allowing this distinction to be made, and incoordinate contraction and relaxation detected and quantified. We have previously shown that these abnormalities may lead to characteristic alterations in the time relations between left ventricular dimensions measured by echocardiography and left ventricular pressure (Gibson and Brown, 1976), particularly when a pressure-dimension loop is constructed. In the present study, we have explored the possibility of substituting the apex cardiogram for the pressure pulse in order to obtain the same information non-invasively. We have, therefore, investigated the time relations between the various phases of the apex cardiogram and the corresponding phases of the high-fidelity left ventricular pressure pulse and of the left ventricular dimension measured by echocardiography.

Subjects

(1) TIME RELATIONS BETWEEN APEX CARDIOGRAM AND LEFT VENTRICULAR PRESSURE

Observations were made in 12 patients with valvular heart disease or cardiomyopathy aged between 13 and 70. In all patients, left ventricular pressure was measured with a Millar micromanometer, mounted on a No. 5 catheter. Apex cardiograms were recorded simultaneously with the patient in the left semilateral position, often with the left arm raised, from the point of maximum impulse. A Cambridge Scientific Instruments transducer was used, with a 3 cm cup, a time constant of 4 s and a lower frequency limit of 0·05 Hz. Pressure, apex cardiogram, and electrocardiogram were recorded photographically with no electrical damping, at a paper speed of 100 or 250 mm/s, using an SE 3012 or EMMA recorder (Fig. 1).

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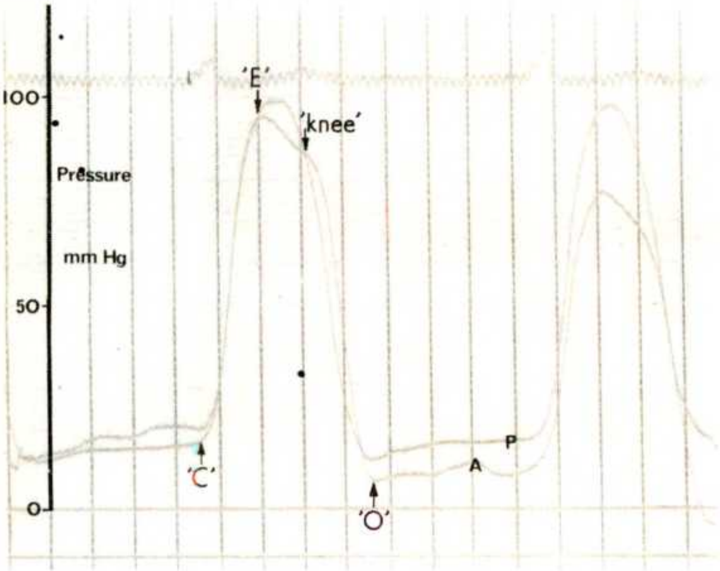

Fig. 1 *Simultaneous left ventricular pressure (P) and apex cardiogram (A) recorded in a patient with aortic regurgitation.*

(2) TIME RELATIONS BETWEEN APEX CARDIOGRAM AND LEFT VENTRICULAR DIMENSION

These studies were based on simultaneous echocardiograms of the left ventricular cavity and apex cardiograms (Fig. 2). Echocardiograms were recorded with a Smith-Kline Ekoline 20 Ultrasonoscope and either a Cambridge or a Honeywell strip-chart recorder at a paper speed of 100 mm/s, using a 2·25 MHz transducer. Echocardiograms showed clear, continuous endocardial echoes, together with those from the mitral valve cusps, and were recorded at the same time as an apex cardiogram.

Fifty-two patients were studied who were in one of 4 groups:

Group A

Twelve normal subjects (10 male). Age range 13 to 56 years, with no clinical or haemodynamic evidence of heart disease.

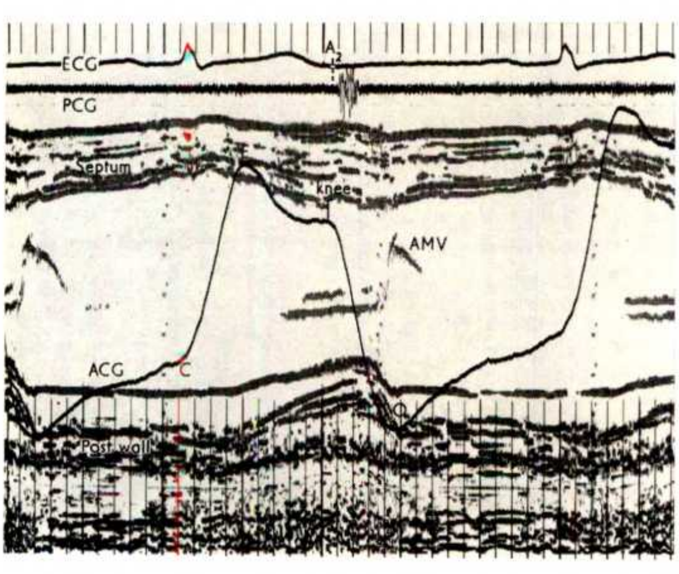

Fig. 2 *Simultaneous apex cardiogram (ACG) and echocardiogram showing septum, posterior wall endocardium and epicardium, and anterior mitral valve leaflet (AML). Simultaneous electrocardiogram (ECG) and phonocardiograms (PCG) are also recorded. A_2 = aortic valve closure.*

Group B

Ten patients with aortic regurgitation. In 9, the severity of the lesion was such as to require aortic valve replacement. All were in sinus rhythm, and none had additional mitral valve disease.

Group C

Ten patients with pure mitral regurgitation, which in 6 was the result of ruptured chordae tendineae, and in 4 was rheumatic. Seven were in atrial fibrillation.

Group D

Twenty patients with significant obstructive coronary artery disease and left ventriculograms showing segmental abnormalities. None had significant mitral regurgitation.

(3) DATA PROCESSING

Echocardiograms, apex cardiograms, and pressure traces were digitised as previously described (Gibson and Brown, 1973), except that a Summagraphics digitiser (20 by 20 in. with 0·01 in. resolution) and a Prime 300 computer system were used. The co-ordinates of the points representing these traces were stored on disc, and used for subsequent calculations.

Apex cardiogram and left ventricular pressure

The data were further analysed to determine the correlation between the upstroke of the pressure pulse and that of the apex cardiogram (from the 'C' point to the 'E' point), and of the downstroke of the pressure and apex cardiogram (from the 'knee' to the 'O' point). The 'C' point is the onset of the upstroke, and the 'E' point the first peak or angulation of the upstroke; the 'knee' is defined as the second peak or angulation on the downstroke of the apex cardiogram, and the 'O' point as the nadir of the downstroke. The digitised apex cardiogram was displayed on a Tektronix 4010 VDU, and the two landmarks on the upstroke or downstroke identified by adjusting a cursor (Fig. 3A). The correlation between the apex cardiogram and the corresponding region of the pressure trace was then calculated. The pressure pulse was next shifted along the time axis by the computer and the correlation with the apex cardiogram calculated again. In this way, graphs of correlation between apex cardiogram and pressure over a range of time shifts were constructed and drawn on a CIL plotter using GINO-F software (Computer Aided Design Centre). From these graphs, the time shift between apex cardiogram and pressure trace, giving maximum correlation between the two, could be determined for each of the selected regions (Fig. 3B).

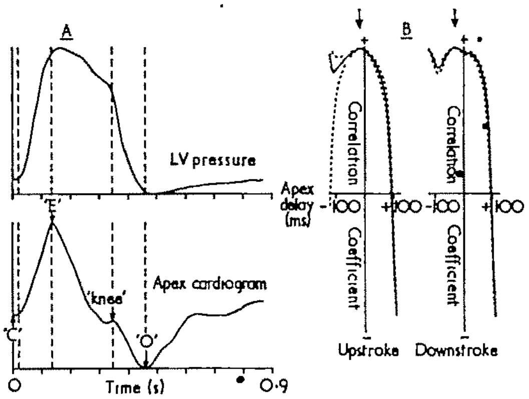

Fig. 3 *(A) Digitised apex cardiogram and left ventricular pressure recordings. Vertical lines, which are defined with respect to the apex cardiogram, represent the 'C' point, 'E' point, 'knee', and 'O' point (see text). (B) Correlation between upstroke (left) and downstroke (right) of apex cardiogram and pressure trace. Peak correlation (arrows) between the two occur on the upstroke when the pressure is delayed by 13 ms (r = 0·995) and on the downstroke when it is delayed by 33 ms (r = 0·997). Limits representing two standard errors of the correlation coefficients are indicated (dotted lines).*

Apex cardiogram and left ventricular dimension

From the digitised data plots were made of left ventricular dimension (D), rate of change of dimension (dD/dt) in cm/s, and normalised rate of change of dimension:

$$\left(\frac{1}{D}\times\frac{dD}{dt}=\mathrm{Vcf}\right)$$

with the units s^{-1}, and also the relation between the apex cardiogram and dimension, in the form of an echo dimension-apex cardiogram loop (Fig. 4). End-diastolic dimension was defined as that at the start of the Q wave of the electrocardiogram of the beat in question, and was taken as zero time. End-systolic dimension was taken as that at the time of minimum separation of the septal and posterior wall echoes. On the echo dimension-apex cardiogram loop, the following measurements were made (Fig. 5).

(i) The change in left ventricular dimension between the start of the upstroke of the apex cardiogram ('C' point) and the 'E' point, expressed as a percentage of the total excursion during the cardiac cycle.

(ii) The percentage change in left ventricular dimension between the start of the downstroke of the apex cardiogram and the minimum dimension.

(iii) The percentage change in left ventricular dimension occurring between minimum dimension and the 'O' point on the apex cardiogram.

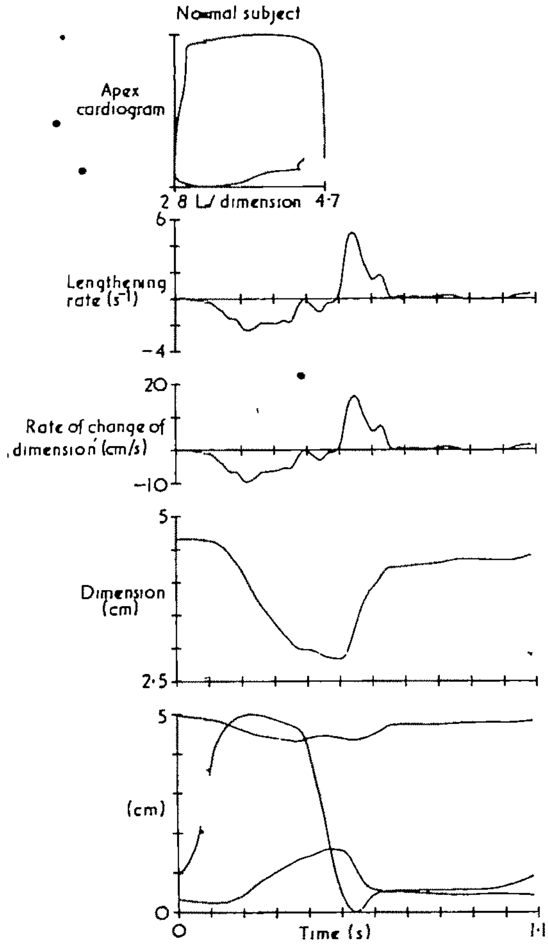

Fig. 4 *Computer output of digitised apex and echocardiogram from a normal subject, representing, from below, the original data showing septum, posterior wall, and apex cardiogram; above are changes in dimension (D), rate of change of dimension (dD/dt), normalised rate of change of dimension* $\left(\frac{1}{D}\times\frac{dD}{dt}\right)$ *and the echo dimension-apex cardiogram loop.*

Statistical analysis was by conventional t tests. Normal values were taken as those lying within a range of ±2 standard deviations of the corresponding mean value in the normal group.

Results

(1) APEX CARDIOGRAM AND LEFT VENTRICULAR PRESSURE PULSE

In all patients studied, there was a small time delay of both the upstroke and the downstroke of the apex cardiogram with respect to the left ventricular pressure. The shift was 17±18 ms (mean±1 standard deviation) for the upstroke and 28±16 ms for the downstroke. The magnitude of the delay in individual patients did not appear to be dependent on the nature or severity of the heart disease present.

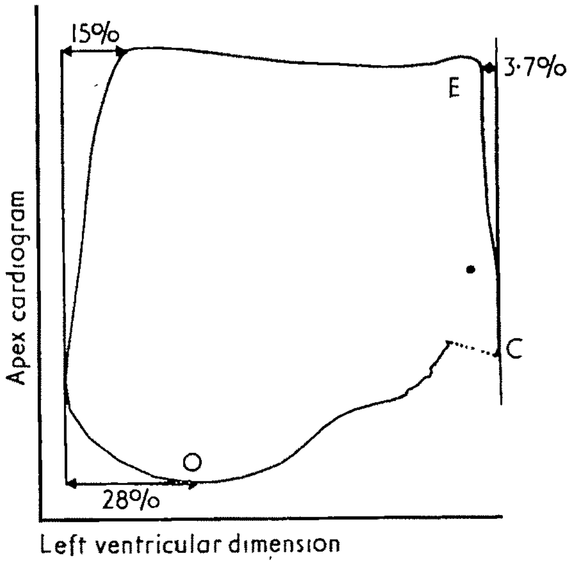

Fig. 5 *Echo dimension-apex cardiogram loop from a normal subject, showing measurements made. 'O', 'C', and 'E' points are indicated, together with changes in dimension during the upstroke of the apex cardiogram, inward movement after the onset of the downstroke, and outward movement before the 'O' point. Measurements are expressed as a percentage of the overall change in dimension during the cardiac cycle.*

(2) APEX CARDIOGRAM AND LEFT VENTRICULAR DIMENSION

Normal subjects

In all normal subjects, the upstroke of the apex cardiogram occurred at a time when there was little or no change in left ventricular dimension. This relation is apparent from direct inspection of the records, but is seen more clearly when an apex cardiogram-echo dimension loop is constructed. The maximum reduction in dimension seen during the upstroke was 15 per cent of the total excursion of wall movement, and the mean value was 6·2±4·9 per cent. Left ventricular dimension did not increase at this stage of the cardiac cycle in any normal subject.

During ejection, when left ventricular dimension was falling, the shape of the apex cardiogram was variable. In the majority of cases, there was a steep descent from the 'E' point to a late systolic plateau, while in others there was slowing declining inward movement, and in 1 case, a late systolic bulge was observed. Because of this variability in normal subjects, no further attempt was made to study apex cardiogram-echo dimension relations at this stage of the cardiac cycle in the other groups of patients.

At the end of ejection, the apex cardiogram presents a sharp angulation downwards, the 'knee', which takes place when left ventricular dimension has almost reached a minimum. A further reduction of $7{\cdot}2 \pm 2{\cdot}9$ per cent total dimension change was found to occur in normal subjects after the time of inscription of the 'knee'. This reduction is not apparent from inspection of the original records, but can readily be measured from the apex cardiogram-echo dimension loop. The apex cardiogram continues to fall at constant dimension for a short period, but before the 'O' point is reached, a significant increase occurs, which accounts for $21 \pm 6{\cdot}8$ per cent of total excursion. The mean duration of the downstroke was 120 ± 16 ms, and during this period septal and posterior wall echoes moved approximately parallel to one another. In 8 patients this movement was away from the anterior chest wall, in 2 towards it, and in 2 no definite direction. The 'O' point of the apex cardiogram occurred 4 ± 10 ms after the time of peak rate of increase of dimension, a value not significantly different from zero, confirming the data of Prewitt *et al.* (1975).

Aortic regurgitation

In this group, the echo dimension-apex cardiogram loop was normal in only 2 patients. In the remainder, characteristic disturbances were present (Fig. 6). There was a mean reduction of left ventricular dimension of $13 \pm 8{\cdot}3$ per cent during the upstroke of the apex cardiogram, which was greater than normal ($P < 0{\cdot}05$), while the reduction in dimension after the onset of the downstroke was less ($2{\cdot}9 \pm 3{\cdot}3$ per cent), being absent altogether in 4 patients. The most prominent abnormality was a considerable increase in dimension before the 'O' point, which accounted for 43 ± 22 per cent of the total excursion ($P < 0{\cdot}01$).

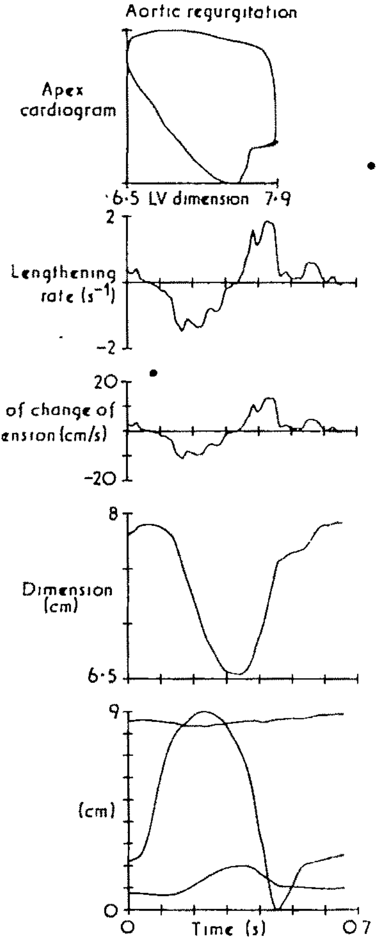

Fig. 6 *Echo and apex cardiogram from a patient with aortic regurgitation. The layout is similar to that of Fig. 4. A considerable increase in dimension has taken place before the 'O' point.*

Mitral regurgitation

In all patients with mitral regurgitation, there was significant reduction in dimension during the upstroke of the apex cardiogram, amounting to 16 ± 9 per cent ($P < 0{\cdot}05$ with respect to normal). In patients in whom the mitral regurgitation was the result of ruptured chordae tendineae, the remainder to the loop was normal (Fig. 7). On the other hand, in those in whom it was the result of rheumatic involvement, there was a very considerable increase in dimension before the 'O' point (55 ± 17 per cent) ($P < 0{\cdot}001$ with respect to normal).

Ischaemic heart disease

A variety of disturbances was present in this group of patients, and in none were echo dimension-apex cardiogram relations completely normal. Though the mean change in dimension during the upstroke was not significantly different from normal, there was considerable scatter, with individual patients lying outside the normal range. In 6, dimension fell significantly during the upstroke by up to 39 per cent (Fig. 8) and in 6, there was an abnormal increase of up to 14 per cent of total excursion (Fig. 9). Similarly, in 5 patients, a greater

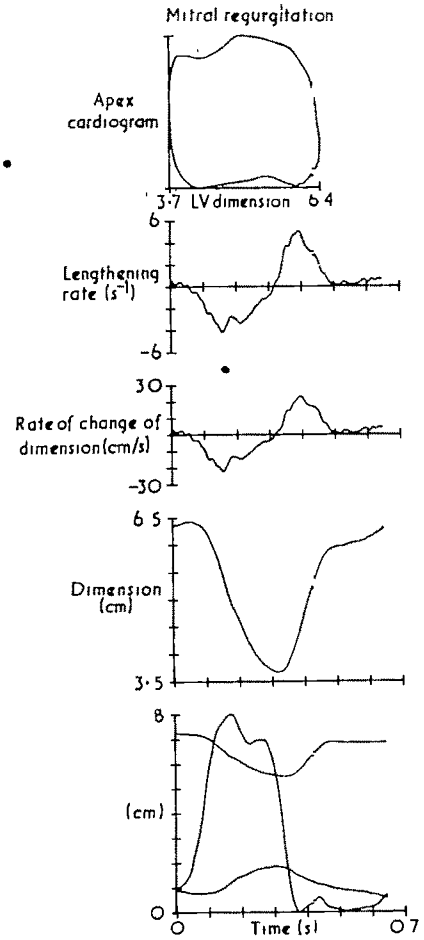

Fig. 7 *Echo and apex cardiogram from a patient with mitral regurgitation. The layout is similar to that of Fig. 4. Significant inward wall movement occurs during the upstroke of the apex cardiogram.*

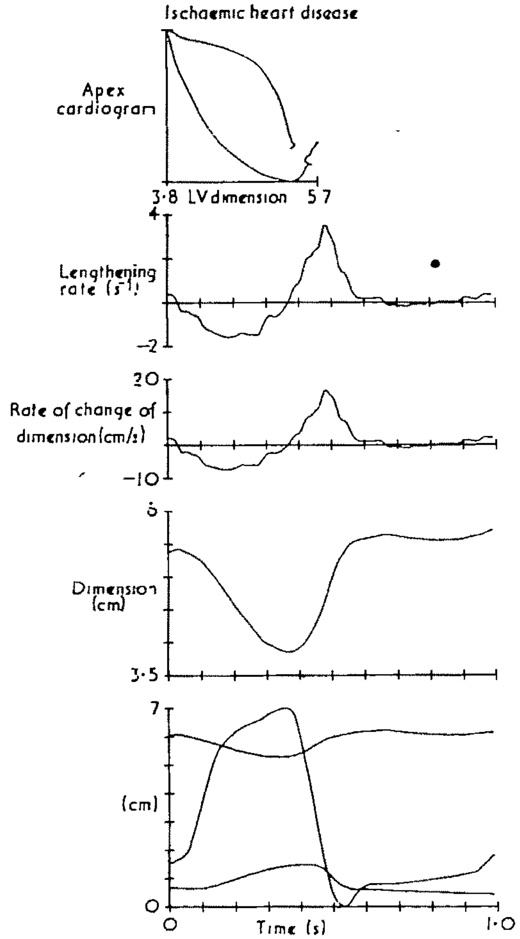

Fig. 8 *Echo and apex cardiogram from a patient with ischaemic heart disease. Significant inward movement of the walls of the ventricle occurs during the upstroke of the apex cardiogram and outward movement before the 'O' point.*

than normal reduction in dimension occurred between the start of the downstroke and the time of minimum dimension, the maximum change observed during this period being 36 per cent. Finally, the increase in dimension before the 'O' point in the group as a whole was very abnormal, being 53 ± 23 per cent ($P < 0{\cdot}001$ with respect to normal); values outside the normal range were recorded in 15 out of the 20 patients, of up to 100 per cent total outward movement. It has previously been shown that an abnormal isovolumic increase in left ventricular dimension may occur before mitral valve opening in patients with ischaemic heart disease (Upton, Gibson, and Brown, 1975). In 13 of the present patients, in whom simultaneous echoes from the mitral cusp and left ventricular cavity were recorded, the percentage change in left ventricular dimension (x) before mitral valve opening was compared with that before the 'O' point (y). This showed that there was a high correlation between the two measurements (Fig 10), given by the equation:—

$$y = 0{\cdot}79x + 30, \quad r = 0{\cdot}87$$

Standard error of estimate = 9·2 per cent.

The value of the intercept of 30 per cent is not significantly different from the normal increase in dimension before the 'O' point.

(3) LEFT VENTRICULAR DIMENSION AND ITS RATE OF CHANGE

Mean values for left ventricular dimension and its present method was used which allowed comparison throughout the periods of isovolumic contraction and early relaxation, and showed small, but consistent differences in timing between them. In all the patients studied, pressure events occurred significantly earlier than the corresponding events on the apex cardiogram. The mechanism for this difference was not clear. It was not the result of the time required for transmission by the transducer used for the apex cardiogram, as this was measured directly and found to be less than 1 ms. It might have been caused in part by delay in transmission through the chest wall, but this cannot have been the sole explanation, particularly in early relaxation.

The apex cardiogram differs significantly from the pressure recording during ejection and also during diastole after the 'O' point. As has been pointed out, the exact configuration of the apex cardiogram during ejection was variable and not clearly associated with other clinical or haemodynamic evidence of left ventricular disease. During filling, discrepancies between the two recordings have considerable clinical significance, though the genesis of the rapid filling wave, the third heart sound point, and the 'a' wave are not clear. We conclude, therefore, that allowing for a small delay of 10 to 30 ms, the apex cardiogram can be used to give the timing of the ventricular pressure trace during isovolumic contraction and early relaxation, but that during filling and ejection there are significant differences between the two.

In the normal subject, the timing of events on the apex cardiogram bears a close relation to those on the recording of the left ventricular dimension. During the upstroke, there is a slight reduction in left ventricular dimension, amounting to approximately 6 per cent of the total excursion, and at least part of this may be accounted for by the fact that the 'E' point of the apex cardiogram occurs slightly after the onset of ejection. During ejection, when the greatest change in dimension occurs, the amplitude of movement of the apex cardiogram is variable, and no consistent pattern emerged. However, at the start of ventricular relaxation, there was a sharp discontinuity in the apex cardiogram ('knee') with a further reduction in dimension. Finally, dimension again increased before the 'O' point, which has previously been shown to correlate more closely with peak rate of increase of dimension than with mitral valve opening (Prewitt *et al.*, 1975). Nevertheless, overall changes in dimension during the downstroke of the apex cardiogram are small, so that during this period of the cardiac cycle, which had a mean duration of 120 ms, septal and posterior wall echoes moved parallel to one another, usually in a posterior direction with respect to a transducer on the anterior chest wall. These relations between apex cardiogram and echo dimension were more clearly apparent when displayed as a loop, whose form, particularly during the periods of the upstroke and the downstroke, resembled those previously constructed between left ventricular pressure and dimension (Gibson and Brown, 1976).

The relations between echo dimension and apex cardiogram were also characteristic in patients with valvular heart disease. In mitral regurgitation, significant reduction in dimension occurred during the upstroke, reflecting backward movement of blood into the left atrium before aortic valve opening (Karliner, Bouchard, and Gault, 1971). Similarly, the abnormal increase in dimension before the 'O' point in aortic regurgitation is likely to be the result of early diastolic filling from the aortic root before mitral valve opening. Simultaneous recording of echocardiogram and apex cardiogram thus allows the abnormal timing of these changes in dimension to be established, thus giving information which is not available from the echocardiogram alone. These changes in dimension may be regarded as analogous to the changes in volume described by Rackley *et al* (1967) in valvular heart disease, and displayed in an exactly similar manner by constructing pressure-volume loops. This similarity depends on the fact that during the upstroke and downstroke, the apex cardiogram reflects the timing of the ventricular pressure pulse, and that contraction and relaxation in these patients with valvular heart disease is co-ordinated, so that the echo dimension can be taken as an index of the behaviour of the ventricle as a whole.

The abnormal relation between echo dimension and apex cardiogram in patients with ischaemic heart disease cannot be explained on these grounds, since none had significant valvular regurgitation. However, all had abnormal left ventricular angiograms, so that the timing of changes in ventricular dimension can no longer be taken as reflecting overall ventricular events. Rather, it seems likely that these abnormal changes in dimension were the result of regional disturbances of function. An increase or decrease in dimension during the upstroke of the apex cardiogram might thus reflect asynchronous onset of contraction (Karliner *et al.*, 1971), with portions of myocardium developing tension early, moving inwards with corresponding outward movement elsewhere during the period of isovolumic contraction. It seems likely that both types of behaviour were observed in the present study. Similarly, during relaxation, the commonest abnormality was increased outward movement before the 'O' point of the apex cardiogram. This might have reflected an isovolumic shape change or abnormally rapid early diastolic filling. The former explanation seems more likely, since there was close correlation between these changes and the extent of outward wall movement before mitral valve opening, which is a direct measure of the severity of the isovolumic disturbance. Such changes have previously been documented angiographically (Altieri *et al.*, 1973; Ruttley *et al.*, 1974; Hamby *et al.*, 1974; Wilson *et al.*, 1975; Gibson *et al.*, 1976), and by echocardiography (Upton *et al.*, 1976).

This disturbed relation between echo dimension and apex cardiogram in patients with ischaemic heart disease and segmental abnormalities of left ventricular function suggests that the method might be used to detect incoordinate ventricular contraction and relaxation. In addition, the echo dimension itself can be used to give information about left ventricular cavity size and instantaneous rates of wall movement. These non-invasive methods, combined with relatively simple data handling techniques can thus be used to study three significant and separable aspects of left ventricular function. It is possible, therefore, that the present method may have applications in other clinical situations.

The computer equipment used in this study was provided by the DHSS as part of their experimental programme.

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Spatial Frank vectorcardiogram in left posterior fascicular block

Criteria and correlation with clinical and electrocardiographic data[1]

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Computer processing of spatial QRS parameters (Frank vectorcardiogram) was used to study left posterior fascicular block. The best set of vectorcardiographic criteria was sought in order to characterise the classic pattern of left posterior fascicular block.

Using these criteria, 18 cases were selected from a group of 4600 patients and 340 healthy subjects; isolated left posterior fascicular block was seen in 10 cases, and was associated with right bundle-branch block in 8 cases.

It is shown that some external factors can influence the aspect of the spatial QRS loop in left posterior fascicular block: cardiomegaly tends to produce a superior displacement of the main QRS forces: right bundle-branch block enhances the superior displacement of the initial forces and shifts the main QRS forces more anteriorly and to the right. The 'masquerading effect' of the left posterior fascicular block on a concomitant inferior myocardial infarct was also shown.

The most important diagnostic feature was the opposite direction of the initial forces (left anterosuperior) and the maximal vector (right postero-inferior): the angle between these two vectors averaged 152°. Other criteria, such as the direction of rotation or the axis of the frontal loop, the vertical direction of the spatial loop, the presence of a Q wave in leads II, III, and aVF of the electrocardiogram, are not mandatory for the diagnosis of left posterior fascicular block.

After the preliminary report of Pryor and Blount (1966), the concept of left fascicular block was introduced by Rosenbaum *et al.* (1968). Many papers have been published on left anterior fascicular block but left posterior fascicular block has been less extensively studied. The latter is much rarer and the sensitivity and specificity of the electrocardiographic criteria of left posterior fascicular block are still uncertain. For instance, rightward deviation of the mean QRS axis, generally considered as a major criterion, is present in other conditions such as right ventricular overload or with a distinctly vertical position of the heart; also, criteria based on the configuration of the initial segment of the QRS lose their validity in the presence of myocardial infarction as this also affects the early part of the QRS complex.

Consequently, there is no consensus about the electrocardiographic criteria of left posterior fascicular block: rightward shift of the mean QRS axis beyond +90° is not required by some authors (Medrano *et al.*, 1972), and leftward orientation of the initial part of the QRS is not mandatory according to others (Fernandez *et al.*, 1972). Indeed, the actual presence of left posterior fascicular block in some reported cases can be questioned.

In this study, a specific methodology has been used in order to avoid the problems resulting from non-validated electrocardiographic criteria for the diagnosis of left posterior fascicular block. The cases of left posterior fascicular block were selected according to several vectorcardiographic criteria

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and a quantitative analysis of the spatial QRS loop was performed; the results of the analysis have been compared with published data.

Subjects and methods

RECORDING TECHNIQUE

In addition to the conventional 12 lead electrocardiogram the vectorcardiograms were recorded using the corrected orthogonal lead system of Frank. The patients were lying in a semirecumbent position, with the thorax at 45° from the horizontal level; the 4th intercostal space was used. The three planar vectorcardiographic loops were directly inscribed on paper by means of a digital system, with a sampling rate of 500 per second (Arnaud *et al.*, 1968). Each patient had a second recording which provided the onset of the QRS with an increased magnification and a sampling rate of 1000 per second. The scalar components X, Y, and Z were simultaneously recorded on an Elema-Schonander electrocardiograph, at a speed of 100 mm/s.

COMPUTER PROCESSING

For each recording, a QRS-T complex was processed by a PDP/8 computer.[1]

The programme 'EXPV', developed in this laboratory, computes 180 vectorcardiographic measurements (Rubel *et al.*, 1975). The spatial QRS loop is characterised in reference to the 8 octants of the tridimensional space, and for each octant the following parameters are computed: the area developed by this segment of curve (absolute area and relative area, that is its percentage of the total QRS area); the duration in this octant (absolute and relative duration); and the maximal octantal vector: in terms of its magnitude (absolute and relative value), its orientation, and its time of occurrence from the onset of QRS. Among the other measurements, the more important are: the maximal spatial and the half-area spatial QRS vectors, their magnitude, orientation, and time of occurrence; the QRS duration and the half-time QRS vector; and the direction of rotation of the planar QRS loops. Thereafter, three different curves are derived as a function of time (sampling at 500 per second): the curve of the amplitude of the spatial instantaneous vectors, the curve of the linear velocity of the spatial QRS loop, and the curve of the elementary areas.

The reference frame for angular values is as follows: the azimuth angle, that is the angle between the projection of a vector on the horizontal plane and the transverse X axis is measured from 0 to 360° in a clockwise direction starting from the left extremity of the X lead. The elevation angle, that is the angle drawn by the spatial vector with the horizontal plane—is measured from 0 to +90° below the horizontal plane and from 0° to −90° above this plane (negative value = superior direction). The 'initial QRS segment' is defined as the vector located at the point having the maximal superior altitude, that is at the highest value of the vertical Y component in its initial deflection.

POPULATIONS STUDIED

(1) A series of 4600 consecutive patients with various heart diseases drawn from the wards of the Cardiovascular Hospital of Lyons.
(2) A group of 340 healthy active subjects.

We excluded from this study cases presenting: (1) right ventricular hypertrophy or overload, suggested by clinical and/or haemodynamic data; (2) chronic obstructive pulmonary disease; (3) a vertical heart on chest *x*-ray examination.

Furthermore, we excluded all the cases where the diagnosis of left posterior fascicular block could not be found for one of the following reasons: (1) QRS duration less than 90 ms; (2) absence of accurate diagnostic information; (3) presence of complete or incomplete left bundle-branch block; (4) presence of a pre-excitation syndrome; (5) anterior, anteroseptal, or anterolateral wall myocardial infarction (which could cause loss of initial anterior forces), or true posterior wall myocardial infarction (because of its peculiar effect on the horizontal QRS loop). Cases of inferior wall myocardial infarction were retained.

PRELIMINARY SELECTION OF VECTORCARDIOGRAMS

A preliminary selection was made on the basis of the following provisional vectorcardiographic criteria, derived from the accepted definition of left posterior fascicular block (Castellanos and Lemberg, 1971; Polu *et al.*, 1972; Pryor, 1972; Varriale and Kennedy, 1972; Chou *et al.*, 1974; Nicolai *et al.*, 1974): (a) initial QRS segment oriented to the left, anteriorly (left anterior quadrant of horizontal plane), and superiorly (left superior quadrant of frontal plane), or sometimes horizontally and to the left in the frontal plane, *and* (b) maximal QRS vector oriented to the right, *or* QRS area greater in the right than in the left half of the electrical field, *or* mean QRS axis of the electrocardiogram equal to or superior to +90°.

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[1] Digital Equipment Corporation.

DEFINITION OF NEW SERIES OF VECTORCARDIOGRAPHIC CRITERIA OF LEFT POSTERIOR FASCICULAR BLOCK

A detailed computer analysis of the various vectorcardiographic measurements was then performed in the cases selected on the basis of these provisional criteria. The results of this analysis combined with additional information collected from electrocardiographic, clinical, and radiological data allowed us to define the following criteria for the electrocardiographic-vectorcardiographic diagnosis of left posterior fascicular block.

Criterion A

The initial deflection of the QRS loop on the vectorcardiogram must be oriented anteriorly, superiorly, and to the left. In the frontal plane, a straight horizontal direction of the early vectors (null value of the elevation angle of the 'first segment vector') is acceptable, provided that both the maximal and the half-area QRS vectors are located in the right half of the electrical field.

Criterion B

Both the maximal and the half area QRS vectors must be oriented to the right, that is located in the right half of the horizontal and frontal planes. The half area vector could be differently oriented, provided that the mean QRS axis of the electrocardiogram was equal to or superior to +90°.

CRITERIA OF AN ASSOCIATED COMPLETE RIGHT BUNDLE-BRANCH BLOCK

For the diagnosis of a complete right bundle-branch block, all the following criteria must be satisfied: (1) QRS duration $\geqslant$115 ms in the adult (94 ms in a 7-year-old child—case 12, see below), (2) delay of the inscription of the late QRS vectors, visualised in all three planes, and (3) presence of a plateau, with or without oscillations, on the late part (beyond 85 ms) of the linear velocity curve of the spatial QRS loop.[1]

DESCRIPTION OF CASES SELECTED

From the hospital population of 4600 patients, 18 cases with evidence of left posterior fascicular block (0·39%) were selected on the basis of these criteria. No cases were found in the group of 340 normal subjects. The 18 records were further divided into 2 groups: group A (10 cases) with isolated left posterior fascicular block (cases 1 to 10); group B (8 cases) with left posterior fascicular block + complete right bundle-branch block (cases 11 to 18).

There were 15 male and 3 female patients whose ages varied from 7 to 91 years. As seen in the study of Lopes *et al.* (1974), the mean age was lower in group A (41·8) than in group B (52·9). The clinical and pathological findings, and the electrocardiographic diagnoses are listed in Tables 1 and 2. Fig. 1A and B present the vectorcardiographic and electrocardiographic features of a 35-year-old patient (case 6) and show the typical orientation of the initial segment vector and the distinct right displacement of the main QRS forces.

Results

The results of the vectorcardiographic and electrocardiographic analyses are presented in Table 3 (group A, isolated left posterior fascicular block; and group B, left posterior fascicular block + complete right bundle-branch block).

The initial segment vector of the spatial QRS loop had an azimuth angle (AZ) varying from 0 to 90°. The mean value was higher in group A than in group B: 57·1°, as opposed to 38·9°.

The elevation angle varied from 0° (straight horizontal orientation in the frontal plane) to −77° (superior orientation). The mean value was lower in group A (−17·1°) than in group B (−33·5°).

The angle between the initial segment vector *and the maximal QRS vector* varied from 75° to 176° (mean=152·9° in group A and 151·9° in group B).

The maximal vector located in the left anterosuperior octant, in the early part of the spatial QRS loop, had a relative magnitude (RM) varying from 6 to 70 per cent of the maximal spatial QRS magnitude. The mean value was 24·3 per cent in group A and 29·5 per cent in group B.

The relative area (RA), that is the area drawn by the initial segment of the spatial QRS loop in the left anterosuperior octant as compared with the total QRS loop area, averaged 3·8 per cent in group A and 3·5 per cent in group B. The value was less than 1 per cent in 4 cases.

The QRS loop remained in this left anterosuperior octant during a period (*absolute duration*) varying from 10 to 52 ms (mean 20·6 ms in group A and 23·4 ms in group B). This represented 6 to 47 per cent of the total QRS loop duration (*relative duration*; mean=20·8% in group A and 16·6% in group B).

The orientation of the maximal QRS vector was mainly toward the right posteroinferior octant of the space. Its azimuth angle was between 146° and 260° (mean in group A 243·7° and in group B 197·6°). Its elevation angle varied from 68° (below the horizontal plane) to −6° (above the horizontal

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[1] In normal individuals, the terminal part of this curve is less delayed and always decreases steeply.

Table 1 *Clinical and pathological findings, electrocardiographic diagnosis of group A; isolated left posterior fascicular block*

Case No.	*Age (y)*	*Sex*	*Clinical and pathological findings*	*Electrocardiographic diagnosis (apart from left posterior fascicular block)*	*PR (ms)*	*Left ventricular enlargement* (x-ray)*
1	18	M	Essential hypertension	Left ventricular hypertrophy	110	—
2	43	M	Hypertension, nephropathy	Left ventricular hypertrophy	140	+
3	13	M	Supraventricular tachycardia-frequent bouts	No WPW syndrome (His bundle recording) transient tachycardia-dependent left bundle-branch block	140	+
4	58	M	Severe calcific aortic stenosis: normal right-sided pressures	Pronounced left ventricular hypertrophy	180	+++
5	69	M	Coronary artery disease; old inferior wall myocardial infarction—left ventricular failure	Incomplete left bundle-branch block	180	—
6	35	M	Severe calcific aortic stenosis; left ventricular hypertrophy, aortic valve replacement—post-surgical syncope	Left ventricular hypertrophy; after surgery right bundle-branch block and shift of QRS axis +20° to +100°	110	—
7	41	F	Catheterisation and pulmonary angiography: negative—during catheterisation junctional (nodal superior) paroxysmal tachycardia	Transient complete right bundle-branch block (with QRS axis +150°) during paroxysmal tachycardia; otherwise isolated left posterior fascicular block	140	—
8	18	M	Primitive cardiomyopathy; left ventricular failure; normal right-sided pressures	Left ventricular hypertrophy	190	+++
9	62	M	Coronary artery disease; several coronary thromboses; left ventricular failure	Incomplete right bundle-branch block with left anterior fascicular block at first; thereafter complete right bundle-branch block with left anterior fascicular block; finally intermittent right bundle-branch block and permanent isolated left posterior fascicular block	230	++++
10	61	M	Hypertension; severe coronary artery disease (necropsy), old inferior wall myocardial infarction, recent septal necrosis; left ventricular hypertrophy	Inferior wall myocardial infarction	140	++++

*For key, see Table 2.

plane) averaging 18·2° in group A and 30·2° in group B.

The orientation of the half-area QRS vector was close to that of the maximal vector: the azimuth angle was in the range of 150° to 324° (mean=250° in group A and 213·9° in group B); the elevation angle varied from 81° to –15° averaging 20·5° in group A and 43·9° in group B.

As with the maximal and the half-area QRS vectors, *the half-time QRS vectors* were most often directed to the right posteroinferior octant (14 cases).

The mean QRS axis in the electrocardiogram varied from +90° to 180° in 15 cases. In the remaining 3 cases it was, respectively, +60°, +80°, and –140°. Its mean value was +112° in group A and +127·5° in group B.

In adults, *the relative area of the spatial QRS loop* developing in the left half of the electrical field is normally greater than 75 per cent of the total QRS area. In these patients, lower values were observed (from 4% to 53%; mean: 35·8% in group A and 24·6% in group B), again demonstrating the rightward deviation of the main QRS forces.

The rotation of the QRS loop in the frontal plane was clockwise in 15 cases, counterclockwise in 1 case, and figure-of-8 in 2 cases. In the horizontal plane, the rotation was counterclockwise in 11 cases and figure-of-8 in the remaining 7 cases.

The QRS duration was 90 ms in 3 cases: we believe that this value is compatible with the diagnosis of left posterior fascicular block. The mean value of the QRS duration was 97·1 ms in group A and 146·5 in group B where a right bundle-branch block was associated with the left posterior fascicular block.

The time of occurrence of the maximal vector, from the onset of the QRS loop, varied from 44 to 105 ms (mean 53 ms in group A, and 72 ms in group B). It was greater than 50 ms in 12 cases (5 of the 10 cases of group A, and 7 of the 8 cases of group B), denoting a delay of the first part of the QRS loop preceding the maximal vector. This part was even longer than that following the maximal vector in 11 of the 18 cases.

The time of occurrence of the half-area vector was somewhat shorter: it varied from 32 to 92 ms, averaging 49·5 ms in group A and 64·9 ms in group B. The average time of occurrence of both the maximal and the half-area vectors was 17 ms greater in group B than in group A.

The magnitude of the maximal spatial QRS

Table 2 *Clinical and pathological findings, electrocardiographic diagnosis of group B: left posterior fascicular block + complete right bundle-branch block*

Case No.	*Age (y)*	*Sex*	*Clinical and pathological findings*	*Electrocardiographic diagnosis (apart from left posterior fascicular block)*	*PR (ms)*	*Left ventricular enlargement (x-ray)*
11	70	M	Hypertension; Adams-Stokes syncope	Isolated complete right bundle-branch block; thereafter complete heart block followed by 4/1 AV block and complete right bundle-branch block + left anterior fascicular block; finally complete right bundle-branch block + left posterior fascicular block	220	—
12	7	M	Mitral regurgitation since birth; normal right-sided pressures	Unusual aspect: QRS in V1, no q in I, aVL, V5, V6	150	+
13	54	M	Adams-Stokes syncope	Intermittent complete AV block; complete right bundle-branch block; later on: regression, only isolated left posterior fascicular block	170	—
14	70	F	Aortic stenosis, hypertension, angina, left ventricular failure	Complete right bundle-branch block, axis deviation undetermined (−140°?)	120	+
15	41	M	Rheumatic mitral regurgitation, hypertension, and glomerulonephritis	Complete right bundle-branch block with right axis deviation	150	+
16	36	M	No history of heart disease; Adams-Stokes syncope	Incomplete and intermittent AV block; complete right bundle-branch block with right axis deviation	170	—
17	91	F	Acute inferior wall myocardial infarction 4 days before vectorcardiogram	Unstable AV block—permanent complete right bundle-branch block; transitory left anterior fascicular block, otherwise left posterior fascicular block with shift of QRS axis −90° to +120°	170	+++
18	54	M	Hypertension, angina, left ventricular failure, normal right-sided pressures	First normal QRS axis and SIQIII pattern; thereafter intermittent right bundle-branch block and shift of QRS axis to +140°. Then complete right bundle-branch block and QRS axis +180°	230	+++

Left ventricular enlargement: — nil; + moderate; +++ severe; ++++ very severe.

vector varied from 1·07 to 2·80 mV, averaging 1·80 mV.

As expected, *the curve of the amplitude of the spatial instantaneous vectors* was delayed in its terminal part in all cases with a right bundle-branch block. But the aspect of this curve was always normal, showing no irregularities, especially in its initial part.

The duration of the PR interval was between 110 and 230 ms (mean value: 163 ms). It was 180 or 190 ms in 3 cases, and 220 or 230 ms in 3 cases.

Discussion

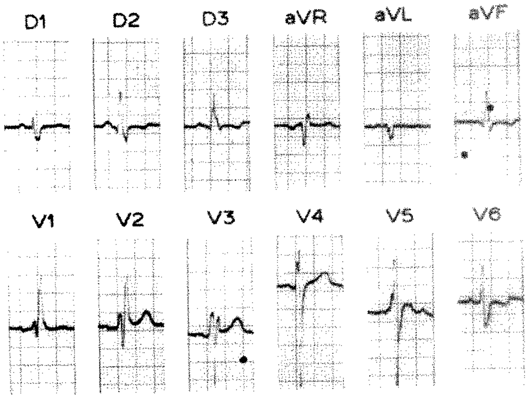
This study confirms that left posterior fascicular block, as diagnosed from vectorcardiographic criteria, is rare whether isolated or associated with right bundle-branch block; it was observed in only 0·39 per cent of the patients in a specialised cardiac institute. Our criteria of selection, with exclusion of all cases with anterior wall myocardial infarction, could account in part for this. The real incidence of left posterior fascicular block in our centre probably approaches 0·45–0·50 per cent, which agrees with the results of others using electrocardiographic criteria (Strickland *et al.*, 1972; Rizzon *et al.*, 1975). In contrast with the left anterosuperior fascicle, which is relatively vulnerable to anterior wall infarction (Rosenbaum *et al.*, 1968; Bobba *et al.*, 1972), we found that left posterior fascicular block was rare in inferior wall myocardial infarction (only 3 cases in our series).

The diagnosis of left posterior fascicular block is difficult, mainly because the commonly used electrocardiographic criteria lack specificity. In this study, we have attempted to define more valid criteria from the Frank vectorcardiogram rather than from the conventional 12 lead electrocardiogram and we have characterised the spatial QRS vector loop in left posterior fascicular block.

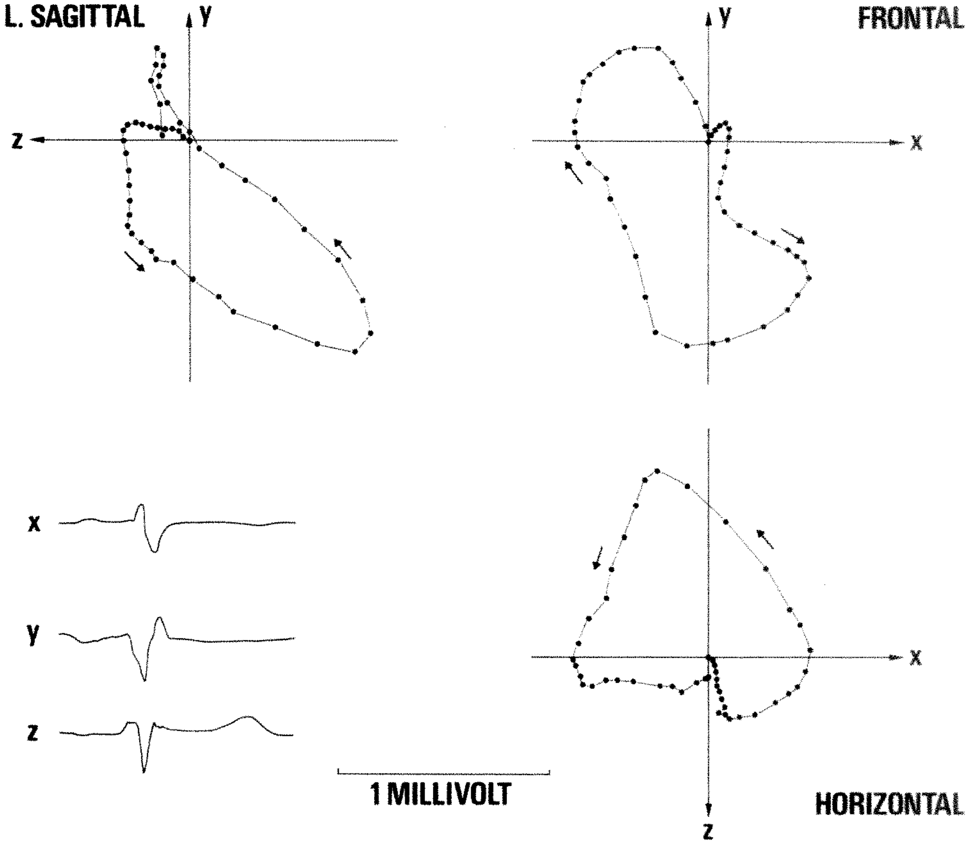
CRITERION A: INITIAL PART OF QRS LOOP

According to criterion A, the initial part of the QRS loop in left posterior fascicular block must be oriented *anteriorly, superiorly,* and *to the left.* This orientation results from the initial depolarisation depending only on the anterosuperior fascicle which activates the anterosuperior part of the left side of the septum and the adjacent anterior left ventricular wall (Scher, 1960; Rosenbaum *et al.*, 1968; Lemberg *et al.*, 1971; Medrano *et al.*, 1971). Right bundle-branch block does not affect this sequence of septal activation (Rosenbaum *et al.*, 1968; Cohen *et al.*, 1968).

In this series, the initial segment of the spatial QRS loop and the maximal spatial QRS vector were oriented in opposite directions. In both groups, these two vectors formed an angle whose mean value was 152°, with a narrow range (140° to 176°, after exclusion of two extreme cases). The presence of complete right bundle-branch block did not modify this particular relation between the initial and the maximal QRS vectors. In group B as compared with group A, the mean elevation angle showed an initial segment vector more superiorly oriented (−33·5° in group B, −17·1° in group A) and a maximal QRS vector more in-



1 B



1A

Fig. 1 *(A) Frank QRS vectorcardiogram (Case 6). Plot time interval of 2 milliseconds. (B) Electrocardiogram, the same patient, who suffered from calcific aortic stenosis with a gradient of 170 mmHg, left ventricular hypertrophy, and poor contractility of both ventricles. After valve replacement (Björk prosthesis), he suffered from syncope, and a demand pacemaker was then inserted. The electrocardiogram before surgery showed left ventricular hypertrophy with a QRS axis of +20° and no ventricular conduction abnormalities. After surgery, right bundle-branch block occurred with a QRS duration of 0·12 s, a shift of QRS axis to +100°, and an SIQIII pattern. (D1, 2, 3 = leads I, II, III.)*

Table 3

Case	*Initial segment vector*			*Left anterosuperior octant*				*Max. vector*				*1/2 area vector*		
No.	*AZ*	*EL*	*Angle with max. vector*	*RM*	*RA*	*AD*	*RD*	*AZ*	*EL*	*T*	*M*	*AZ*	*EL*	*T*
Vectorcardiographic and electrocardiographic values of group A (isolated left posterior fascicular block)														
1	82	−40	163	27	5	26	25	247	58	54	2·80	279	60	48
2	72	−16	168	28	1	20	22	256	4	50	2·11	270	13	40
3	90	−33	154	16	0	13	14	257	11	50	2·32	264	28	40
4	39	0	161	18	1	12	13	253	4	63	2·63	261	4	50
5	0	−21	91	9	0	12	12	260	35	45	1·82	260	35	45
6	80	− 7	142	21	1	18	17	253	44	56	1·37	253	44	56
7	53	−15	165	17	1	20	22	248	21	48	1·51	248	21	48
8	67	−22	173	17	1	13	14	241	15	45	1·42	242	7	50
9	45	0	172	20	2	20	22	232	−4	55	1·07	228	0	50
10	43	−17	140	70	26	52	47	190	−6	64	1·10	195	−7	68
Mean	57·1	−17·1	152·9	24·3	3·8	20·6	20·8	243·7	18·2	53	1·81	250	20·5	49·5
Vectorcardiographic and electrocardiographic values of group B (left posterior fascicular block + complete right bundle-branch block)														
11	11	−65	170	33	3	24	14	214	68	63	2.36	324	81	49
12	24	−11	149	50	3	18	19	233	26	44	2·13	257	46	32
13	64	−42	168	43	13	43	34	226	46	75	2·01	225	50	70
14	54	− 6	158	25	1	16	11	213	13	60	1·65	198	9	72
15	68	−37	75	59	7	35	23	146	0	105	1·07	191	68	68
16	90	−77	154	6	0	28	16	197	55	98	2·70	186	74	92
17	0	−30	176	8	0	13	10	185	34	53	2·29	180	38	48
18	0	0	165	12	1	10	6	167	0	78	1·44	150	−15	88
Mean	38·9	−33·5	151·9	29·5	3·5	23·4	16·6	197·6	30·2	72	1·96	213·9	43·9	64·9

AZ = azimuth angle (°); EL = elevation angle (°); RM = relative magnitude (%); RA = relative area (%); AD = absolute duration (ms); RD = relative duration (%); T = time of occurrence of this vector from onset of QRS (ms); M = magnitude of the maximal vector (mV); 1/2 Time vector = location of the half time QRS vector; RPI = right posteroinferior; LPI = left posteroinferior; RAI = right anteroinferior; RPS = right posterosuperior; RAS = right anterosuperior; FP = frontal plane; HP = horizontal plane; CW = clockwise; CCW = counterclockwise.

feriorly oriented (30·2° in group B, 18·2° in group A). The mean azimuth angle showed that in group B, the initial vectors were less anterior and more leftwards (38·9° in group B, 57·1° in group A) and the maximal vector was more anterior and rightwards (197·6° in group B, 243·7° in group A).

In 3 cases, the initial segment was transversely rather than superiorly oriented (null value of the elevation angle). At the same time, the value of the elevation angle of the maximal vector was very low (4°, 0°, and −4°, respectively). Therefore, in these 3 cases, the opposite direction of the initial and maximal vectors remained as apparent. Thus a null value for the elevation angle of the early QRS forces is compatible with criterion A.

The importance of the initial forces developing in the left anterosuperior octant, as determined by the magnitude of the maximal octantal vector, as well as by the area and duration of these forces, was found to be variable. There are some external factors which can interfere with the magnitude of these initial vectors in left posterior fascicular block. First, possible interaction from an *inferior wall myocardial infarction* has rarely been discussed (Castellanos *et al.*, 1972). Isolated inferior wall myocardial infarction generally increases the initial QRS forces located in the left anterosuperior octant. Medrano *et al.* (1971) showed in dogs that the production of left posterior fascicular block could decrease or even mask the electrocardiographic-vectorcardiographic signs of a coexisting inferior wall myocardial infarction; Bobba *et al.* (1972) reported 2 cases where left posterior fascicular block during an exercise test occurred concomitantly with decrease of the pathological q waves in leads II, III, and aVF.

In our series, there were 3 cases of inferior wall myocardial infarction. The tracing of case 10 is difficult to analyse in this respect. In 2 cases (5 and 17), the usual vectorcardiographic criteria of inferior wall myocardial infarction were not fulfilled; moreover, the duration of the initial forces was shorter (12 and 13 ms), the area developed by these forces was smaller (< 1%) and their magnitude was lower (8 and 9%) than the average for the total group.

This 'masquerading effect' of a left posterior fascicular block on concomitant inferior wall myocardial infarction can be explained by the pathophysiology of this type of intraventricular conduction defect: when the left posterior fascicular block develops, the initial left activation relies solely on the anterosuperior fascicle, therefore ignoring the posteroinferior wall. If the latter is

Left/total area (%)	*1/2 time vector*	*QRS duration (ms)*	*Rotation*		*QRS axis (°)*	*Q or q in all II, III, aVF*	*SIQIII pattern*
			FP	*HP*			
52	RPI	98	CW	CCW	90	+	+
53	RPI	90	CW	CCW	90	+	+
43	RPI	95	CW	CCW	110	+	+
36	LPI	95	8	CCW	60	—	+
44	RPI	100	CW	CCW	80	+	+
39	RPI	108	CW	CCW	100	—	+
17	RPI	90	CW	CCW	110	+	+
4	RPI	95	CW	8	170	+	+
44	RPI	90	CW	8	130	—	—
26	RPS	110	CCW	8	180	+	+
35·8		97·1			112		
52	RPI	170	CW	CCW	100	+	+
41	RPI	94	CW	8	90	—	+
14	RPI	125	CW	8	100	+	+
12	RPI	148	CW	CCW	-140	+	+
40	RPI	150	CW	8	100	+	+
16	RPI	175	CW	CCW	110	+	+
11	RAI	130	CW	8	120	+	+
11	RAS	180	8	CCW	180	—	+
24·6		146·5			127 5		

injured, the electrical signs of the inferior infarction will not appear. Thus left posterior fascicular block can reduce or even suppress the signs of coexisting inferior wall myocardial infarction.

It was also found in this study that an *associated right bundle-branch block* would increase the importance of the initial QRS forces of left posterior fascicular block. After exclusion of the 3 cases of inferior wall myocardial infarction, the mean values for group B (with right bundle-branch block) as compared with group A (without right bundle-branch block) were, respectively, 32·5 per cent and 20·5 per cent for the magnitude of the maximal octantal vector, 4 per cent and 1·5 per cent for the relative area, and 24·9 ms and 17·7 ms for the duration of this initial segment. We, therefore, suggest that right bundle-branch block in itself can increase the initial forces developing in the left anterosuperior quadrant, and its association with a left posterior fascicular block tends to produce a cumulative effect.

As far as the electrocardiographic diagnosis of left posterior fascicular block is concerned, most authors require *the presence of q waves* in the inferior leads (Rosenbaum *et al.*, 1968; Cohen *et al.*, 1968; Benchimol and Desser, 1971; Tricot *et al.*, 1971; Castellanos *et al.*, 1971; Medrano *et al.*, 1972) or at least in lead III (Kulbertus, 1972), whereas others do not require this (Pryor and Blount, 1966; Fernandez *et al.*, 1972). In our study, a q or Q wave was present in all 3 inferior leads in 13 out of 18 cases; it was found in leads II and III in 1 case, and in lead III only in 3 cases; no q wave was observed in 1 case: in this latter case as in 2 of the 3 cases with a q wave only in lead III, the elevation angle had a null value. As the initial segment can be transversely oriented, left posterior fascicular block could thus be diagnosed in the absence of a q wave in leads II, III, and aVF, provided that the maximal vector and the initial vectors lie in opposite directions, as discussed above.

CRITERION B: MAIN PART OF QRS LOOP

The deviation to the right of the main QRS forces is considered by most authors as the essential criterion for the diagnosis of left posterior fascicular block. This right axis shift is caused by a delay in the activation of the posterobasal region of the left ventricle. The right bundle-branch block is responsible for the delay in the inscription of the right terminal forces, but it will not significantly affect the main part of the QRS. In order to quantify this right axis deviation, we have analysed the orientation of three vectors. The *maximal QRS vector* was directed to the right in all cases (azimuth angle between 90° and 270°). *The half-time vector* was also directed to the right in all but one case. *The half-area* vector was not oriented to the right in 3 of the 18 cases. However, in these 3 cases, the ratio of the left area of the spatial QRS loop over the total QRS area was hardly greater than 50 per cent (52, 52, and 53%, respectively), and the mean QRS axis was at +90° or +110°, therefore fulfilling criterion B.

The individual values of the azimuth angle of both the maximal and half-area vectors showed a wide dispersion, mainly in the right posterior quadrant. These values were in general lower in group B than in group A (a difference of 46° for the maximal vector and 36° for the half-area vector). It can be concluded that, in the presence of left posterior fascicular block, right bundle-branch block produces an additional effect on the QRS loop, shifting the main forces slightly more anteriorly and to the right.

The values of the *mean QRS axis of the electrocardiogram* were also widely scattered. There was a slight difference between group A and B: in group B, the mean value was 15° more to the right. In 3 cases, though the vectorcardiogram was characteristic for left posterior fascicular block, the mean QRS axis was not located in the right inferior quadrant of the frontal plane: it was, respectively, at +60°, +80°, and undetermined (around −140°). This is not surprising since there is not always a good correlation between the orientation of the maximal spatial QRS vector and the angle of the maximal vector in frontal plane (Lopes *et al.*, 1974). Moreover, since the range of normality is different between the mean QRS axis of the electrocardiogram and the angle of the maximal QRS vector in the frontal plane, the criteria for left posterior fascicular block based on these two values should necessarily be different (Poblete *et al.*, 1974).

Although this series is too small to permit a detailed statistical analysis, we have examined other factors that might influence the orientation of the QRS loop in left posterior fascicular block. Five parameters were studied: the azimuth and elevation angles of both the maximal and half-area vectors, and the mean QRS axis of the electrocardiogram. There was no apparent correlation with left ventricular hypertrophy, inferior wall infarction, or the position of the heart within the thorax as judged from chest *x*-ray films. Two factors seemed, however, to play a significant role: (1) *the presence of complete right bundle-branch block* and (2) *the degree of cardiomegaly*. On the basis of the cardiothoracic ratio, we have considered 4 degrees of cardiomegaly: nil, moderate, severe, and very severe. The elevation and azimuth angles represent the average values of both the maximal and half-area vectors.

Fig. 2A shows that cardiomegaly is associated with a decrease of the elevation angle and, therefore, with a more horizontal loop. The cases with right bundle-branch block have higher values of the elevation angle, corresponding to more vertical loops. But in these cases, the cardiomegaly acts in the same way: in advanced stages, it brings the elevation angle toward a null value.

In Fig. 2B, it can be seen that cardiomegaly is also associated with a decrease of the azimuth angle

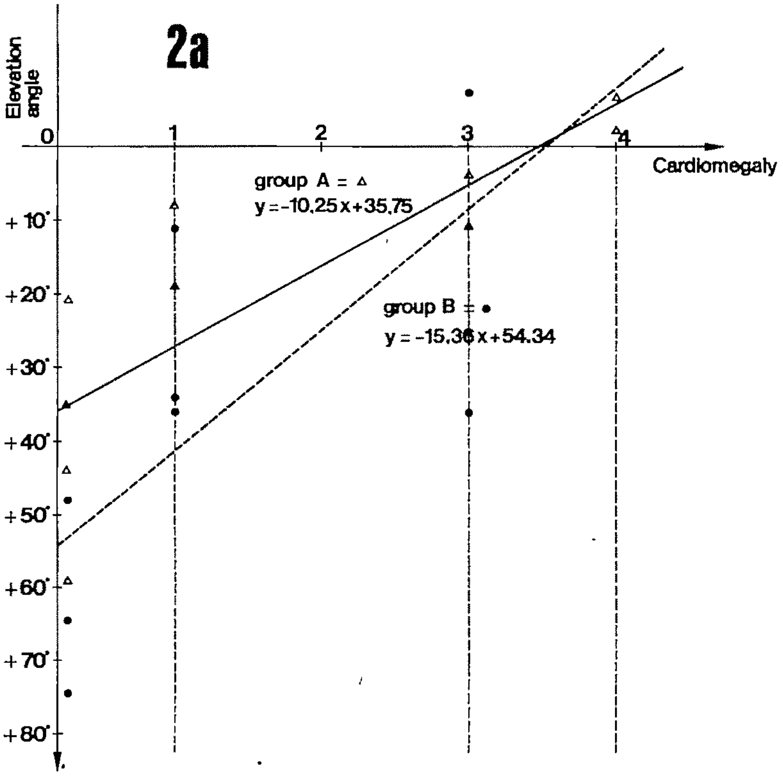
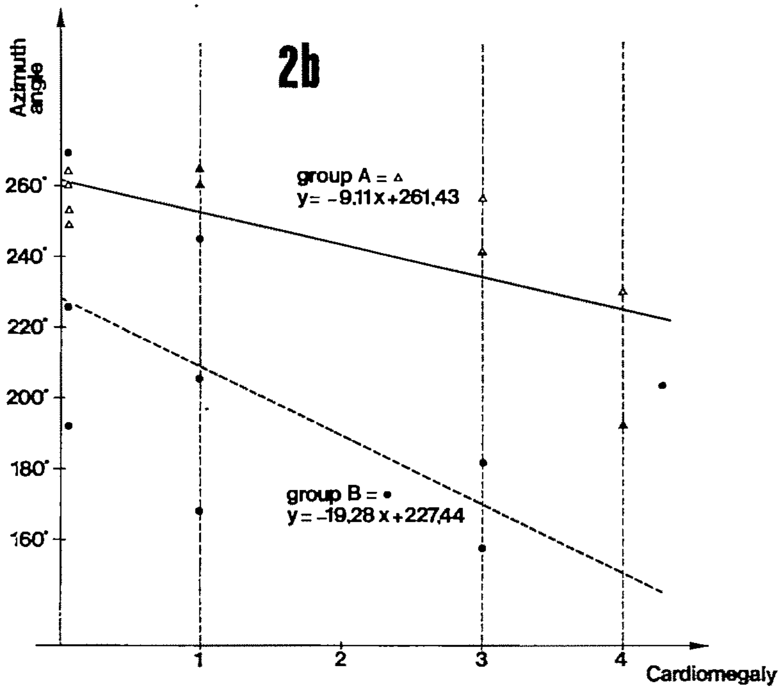
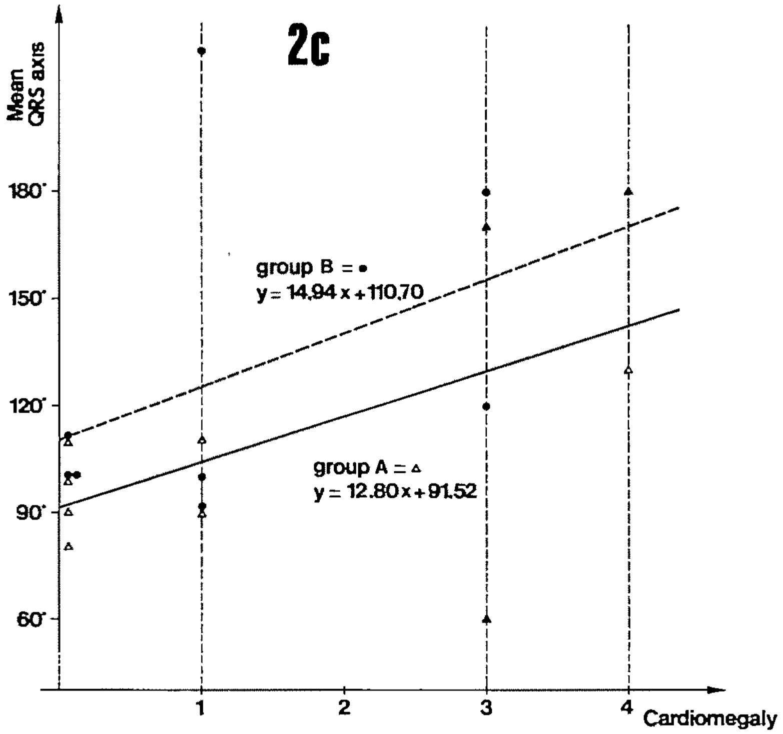


Fig. 2 *Orientation of the main QRS forces as related to the degree of cardiomegaly (abscissa). Individual values of group A (isolated left posterior fascicular block)* = △. *Individual values of group B (left posterior fascicular block + complete right bundle-branch block)* = ●. *Best fitting line for group A* = —— *and for group B* = – – – *(least square method). (a) Ordinate: average of the individual values of the elevation angle of both the maximal and half-area vectors. (b) Ordinate: average of the individual values of the azimuth angle of both the maximal and half-area vectors. (c) Ordinate: individual values of mean QRS axis of the electrocardiogram.*


2b
Azimuth angle
260°
240°
220°
200°
180°
160°
group A = △
y= -9.11x+261.43
group B = •
y= -19.28x+227.44
1
2
3
4
Cardiomegaly


2c
Mean QRS axis
180°
150°
120°
90°
60°
group B = •
y= 14.94x+110.70
group A = △
y= 12.80x+91.52
1
2
3
4
Cardiomegaly

and thus with displacement of the loop to the right and anteriorly. The cases with right bundle-branch block already had lower values of the azimuth angle: in these cases, the cardiomegaly adds its own effect to the anterior shift of the QRS loop. This is shown in the figure by the divergence of the two straight lines.

Fig. 2C shows a similar effect: cardiomegaly is responsible for a rightward shift of the mean QRS axis, even more obvious in cases with right bundle-branch block.

The presence of cardiomegaly tends to decrease the values of both the azimuth and the elevation angle of the main QRS forces. In 3 cases in this series, the latter had a negative value (loop being superiorly oriented). This shows the important influence of cardiomegaly which can produce a superior displacement of the QRS loop in some cases of left posterior fascicular block. Therefore, one cannot retain the inferior orientation of the QRS as a valid criterion of left posterior fascicular block. This is why our *criterion B does not consider the elevation angle,* but only the azimuth angle, i.e. the rightward deviation of the QRS.

Most previous publications stated that the direction of the rotation of the frontal QRS loop is usually clockwise in left posterior fascicular block. This clockwise rotation was observed in 15 cases of our series. It was counterclockwise in 1 case (case 10) and showed a figure-of-8 in 2 cases (cases 4 and 18). But in these 3 cases there was important cardiomegaly, and the elevation angle was low or even negative (between +4° and −15°). Therefore, just as the elevation angle could be influenced by other factors, the rotation of the frontal QRS loop should not be considered among the vectorcardiographic criteria of left posterior fascicular block.

PRESUMPTIVE CRITERIA OF LEFT POSTERIOR FASCICULAR BLOCK

In addition to the vectorcardiographic criteria A and B, the diagnosis of left posterior fascicular block in this series was supported by several other considerations which represent useful presumptive criteria.

(1) *Atrioventricular block (AV block)*

Four patients had a history of Adams-Stokes syncope. The duration of the PR interval was 180 ms or more in 6 patients. In 3 others, there was transient complete or incomplete AV block. The mean value of the PR interval was slightly greater in group B (172 ms) as compared with group A (156 ms).

(2) *Progressive or variable intraventricular conduction defects*

These, which were present in 10 of our patients, appear to be of great diagnostic value. In 6 cases, there was a transient conduction defect such as right bundle-branch block, left bundle-branch block, or AV block of various degree, which disappeared during the follow-up period or was replaced by another type of conduction defect. In 4 cases, the conduction defect progressed and became permanent.

The condition known as *'hémibloc à bascule'*, i.e. left anterior fascicular block evolving into left posterior fascicular block (Rosenbaum *et al.*, 1969a, b) was found in 3 patients (cases 9, 11, 17) who had in addition partial AV block.

(3) *Paradoxical right axis deviation*

In subjects with clinical conditions usually causing left axis deviation, such as a horizontal heart or left ventricular hypertrophy, the paradoxical finding of right axis deviation strongly suggests the existence of left posterior fascicular block. This was the case in half of our patients who had a left ventricular overload.

OTHER CRITERIA OF LEFT POSTERIOR FASCICULAR BLOCK

According to Watt and Pruitt (1969) and Medrano *et al.* (1972) the QRS duration can be slightly increased by about 10 ms, in isolated left posterior fascicular block. In group A of this series, the mean QRS duration was 97 ms. However, cases with a QRS duration less than 90 ms had been excluded from this study (see methods). On the other hand, the 4 patients in group A who displayed a QRS duration longer than 95 ms had left ventricular hypertrophy or myocardial infarction: these conditions could account for a slight increase in the QRS duration. Therefore isolated left posterior fascicular block does not in itself seem significantly to increase the QRS duration. This is also supported by the fact that in group A there was apparently no significant delay of the late portion of the QRS loop in any planar projection, nor was there any delay on the curve of the linear velocity of the spatial vector.

The presence of right ventricular hypertrophy or overload makes the diagnosis of left posterior fascicular block impossible. The most usual pattern (type c) of right ventricular hypertrophy with a QRS loop orientated *posteriorly and to the right* is quite similar to the left posterior fascicular block pattern, and distinction is impossible on the basis of electrocardiographic or vectorcardiographic criteria alone (Strickland *et al.*, 1972). On the other hand, in more severe cases of right ventricular hypertrophy, with a distinct rightward and *anterior* displacement of the mid and late parts of the QRS loop, the diagnosis of right ventricular hypertrophy is more obvious, though left posterior fascicular block could still be associated with the right ventricular hypertrophy.

The *SIQIII pattern* has been considered by some authors as characteristic of left posterior fascicular block. Rosenbaum *et al.* (1969b) reported several cases where the SIQIII pattern occurred concomitantly with intermittent left posterior fascicular block. In fact, our criteria A and B, as previously described, correspond respectively to the existence of a Q wave in lead III and an S wave in lead I. These electrocardiographic criteria were present in all but one patient. However, right ventricular overload is another possible cause o SIQIII pattern (Strickland *et al.*, 1972). Later Scott (1971) suggested that acute cor pulmonale could lead to myocardial ischaemia, which, in turn, could induce transient left posterior fascicular block.

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Echocardiographic assessment of left ventricular function in coronary arterial disease

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This investigation was designed to determine the role of echocardiography in the assessment of left ventricular function in patients with significant coronary arterial disease. Satisfactory echocardiograms were obtained in 43 patients with coronary arterial disease. The ventriculographic ejection fraction was determined by the area length method. The echocardiographic left ventricular end-diastolic dimension was increased to more than 5·4 cm in 17 patients. Fifteen of these patients had an ejection fraction of 0·45 or less. Three patients had a normal left ventricular end-diastolic dimension but an ejection fraction of less than 0·45. Twenty-three patients had an ejection fraction of more than 0·45 and a normal left ventricular end-diastolic dimension. The left ventricular end-diastolic dimension index was increased (>3 cm/m^2) in 15 patients, all of whom had ejection fraction of less than 0·45. Three patients had a normal left ventricular end-diastolic dimension index and an ejection fraction of less than 0·45. Twenty-five patients had a left ventricular end-diastolic dimension index of less than 3 cm/m^2 or less and an ejection fraction of more than 0·45. The percentage fractional shortening of the echocardiographic left ventricular dimension was reduced in 25 patients. In 18 of these the ejection fraction was 0·45 or less. The percentage fractional shortening of the left ventricle was normal in 18 patients. In 2 of them the ejection fraction was less than 0·45. In summary, increase of the left ventricular end-diastolic dimension or left ventricular end-diastolic dimension index is usually associated with a critical reduction of the ejection fraction as determined by ventriculography. Since the ejection fraction is an important determinant of mortality related to bypass graft surgery, echocardiography should be useful in the detection of patients with a poor prognosis.

Echocardiography has proved to be a valuable non-invasive tool in the assessment of patients with valvular heart disease and congenital anomalies of the heart (Zaky *et al.*, 1968; Feigenbaum, 1972; Chung *et al.*, 1973; Popp *et al.*, 1974). The usefulness of this technique in the evaluation of left ventricular function has been established (McDonald *et al.*, 1972; McDonald and Hobson, 1974; Quinones *et al.*, 1974). Recent studies have shown that echocardiography may be used to detect abnormalities of left ventricular wall motion, in patients with coronary arterial disease (Jacobs *et al.*, 1973; Corya *et al.*, 1974a).

Aortocoronary saphenous vein graft surgery has been shown to produce symptomatic improvement in the majority of patients with angina pectoris (Spencer, 1970). The mortality associated with this operation is considerably higher in those patients who have poor left ventricular function (Committee on Coronary Artery Surgery, 1972; Cohn *et al.*, 1974). Thus, the ability to predict poor left ventricular function in such patients by a non-invasive method would be of considerable value. This investigation was designed to determine whether an increase in the echocardiographic left ventricular dimension reflects a critical reduction of the ejection fraction.

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Methods

Echocardiography was performed on 43 patients who underwent cardiac catheterisation for symptomatic coronary arterial disease. Patients with mitral regurgitation were excluded from the study. One of the patients was in congestive cardiac failure and all the patients were in sinus rhythm at the time of the study. Significant stenosis ($>75\%$) of one or more coronary arteries was detected by coronary arteriography in 37 patients. Six patients did not have coronary angiography (because severe left ventricular dysfunction was present on the left ventriculogram) but had a past history of a well-documented myocardial infarction. The patients were examined in the supine position. The echocardiograms were performed within 24 hours of the catheterisation studies. A 2·25 MHz, 1·27 cm, 10 cm focus transducer, an Ekoline 20 ultrasonoscope, and an Electronics for Medicine DR8 recorder were used. The only criterion for patient selection was a technically adequate recording, on which left ventricular echoes could be clearly identified. Satisfactory tracings were obtained in 71 per cent of all patients studied; thus, the 43 subjects of the study were selected from a group of 60 consecutive patients. Left ventricular cineangiocardiography was performed in the right anterior oblique projection. The left ventricular volume and the ejection fraction were calculated using the area-length method (Sandler and Dodge, 1968).

The echocardiographic measurements of the left ventricular dimensions were made at a level just caudal to the mitral valve. The left ventricular end-diastolic dimension (LVED) was measured at the apex of the R wave of the electrocardiogram. The left ventricular end-systolic dimension (LVES) was measured as the shortest recorded distance between the left ventricular septal and posterior wall endocardial echo. The thicknesses of the septum and of the left ventricular posterior wall were measured as previously described by Corya *et al.*, 1974b. The percentage fractional shortening of the left ventricular dimension (%FSLV) was calculated as follows:

$$\frac{(\text{LVED}-\text{LVES})}{\text{LVED}} \times 100.$$

The echocardiographic measurements were made by averaging five consecutive beats in which the endocardial echoes from the septum and posterior wall were clearly seen. The various measurements were made by two observers. The beat-to-beat variation was 2 mm or less. The interobserver variation was also 2 mm or less.

Results

The results are given in the Table. There were 34 men and 9 women. Their ages ranged from 35 to 66 years. Fig. 1 shows the relation between the ventriculographic ejection fraction and the left ventricular end-diastolic dimension (LVED) determined by echocardiography. An ejection fraction of 0·45 or less was taken as evidence of significant left ventricular dysfunction (Committee on Coronary Artery Surgery, 1972).

Values obtained in our laboratory from 32 normal subjects (25 men and 7 women) have been used as normal for the purpose of this paper.

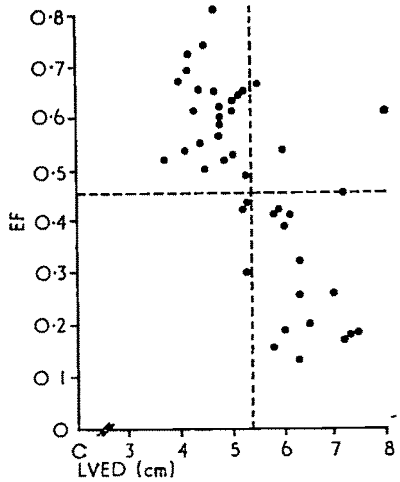

Fig. 1 *The relation between the echocardiographic left ventricular end-diastolic dimension (LVED) in cm and the ventriculographically determined ejection fraction (EF). The vertical dotted line indicates the upper limit of normal (5·4) for the LVED. The horizontal dotted line corresponds to an ejection fraction of 0·45. The correlation coefficient is –0·78.*

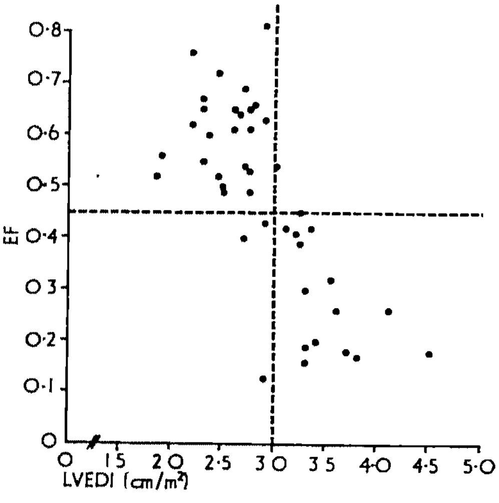

Fig. 2 *The relation between the left ventricular end-diastolic dimension index (LVEDI) in* cm/m^2 *and the ejection fraction. The vertical dotted line corresponds to the upper limit of normal (3* cm/m^2*) for the LVEDI. The correlation coefficient is –0·73.*

Table

Case no.	*Age*	*Sex*	*EF*	*LVEDVI*	*LVED*	*LVEDI*	*LVPWE*	*IVSE*	*%FSLV*	*CAD*
1	51	M	0·56	46	4·8	1·85	1·1	0·7	32	RCA, LAD, CCA, Marg
2	64	M	0·18	116	7·4	3·7	0·2	1·2	19	LAD, CCA, RCA
3	50	M	0·53	84	5·0	2·75	1·3	1·0	46	LAD, RCA
4	58	M	0·32	96	6·3	3·56	1·7	0	21	LAD, Marg
5	52	M	0·41	126	6·0	3·2	0·7	P	12	CCA, RCA, LAD
6	44	M	0·26	132	6·3	3·6	1·0	0	25	LAD, RCA
7	43	M	0·64	65	5·1	2·66	1·3	1·0	39	CCA, RCA, LAD
8	44	M	0·61	83	5·0	2·75	1·3	1·2	44	CCA, RCA, LAD
9	61	F	0·61	54	4·3	2·6	1·6	0·8	51	CCA, RCA, LAD
10	48	M	0·43	90	5·3	2·9	0·3	0·7	17	RCA, LAD
11	35	M	0·5	67	4·5	2·5	0·8	0·7	33	RCA, LAD, Marg
12	60	M	0·42	73	5·9	3·35	1·9	0	32	CCA, LAD, RCA
13	47	F	0·63	61	5·0	2·9	1·3	0	14	LAD, Diag
14	56	M	0·54	87	6·0	3·0	0·8	0·9	28	CCA, RCA
15	57	M	0·65	116	4·7	2·6	1·1	0	28	CCA, RCA, LAD
16	38	M	0·65	89	5·2	2·75	1·0	1·2	40	RCA, LAD
17	54	F	0·54	93	4·1	2·7	1·1	0·4	37	RCA, LAD
18	56	M	0·39	96	6·0	3·24	0·3	0·9	20	—
19	53	M	0·67	76	4·0	2·3	1·2	0·4	40	CCA, RCA, LAD
20	61	M	0·19	114	6·0	3·3	0·3	0·8	16	—
21	40	M	0·17	155	7·3	3·8	1·7	0	19	—
22	57	M	0·6	59	4·8	2·35	1·0	0·3	27	RCA, LAD, Marg
23	60	M	0·49	55	5·3	2·76	1·4	0·9	44	CCA, RCA, LAD
24	58	M	0·52	71	3·7	1·85	1·7	0	38	LAD
25	52	F	0·69	63	4·2	2·7	1·7	0·6	45	LAD, Diag
26	66	F	0·82	56	4·7	2·9	1·2	0·9	38	CCA, RCA, LAD
27	64	M	0·2	161	6·5	3·4	1·0	0·8	15	CCA, RCA, LAD
28	47	M	0·55	51	4·4	2·3	0·8	0·5	27	RCA, LAD, Marg
29	49	M	0·65	90	4·4	2·3	1·0	0·7	32	RCA, LAD, Diag
30	63	F	0·3	121	5·3	3·3	1·0	0·7	30	MLCA, LAD, RCA
31	53	M	0·13	94	6·3	2·9	1·7	0	28	LAD, RCA
32	44	M	0·66	62	5·5	2·8	1·0	0·8	33	RCA, LAD, Marg
33	62	F	0·42	69	5·2	3·1	1·3	0·4	27	CCA, RCA, LAD
34	46	M	0·40	96	5·8	2·7	0·8	0·8	28	CCA, LAD
35	58	M	0·16	159	5·8	3·3	0·3	0·8	16	—
36	66	M	0·49	75	5·3	2·5	1·1	0	17	CCA, LAD
37	46	M	0·75	65	4·5	2·2	1·6	0	33	CCA, LAD, RCA
38	40	M	0·26	135	7·0	4·1	0·7	1·2	26	—
39	46	M	0·45	140	7·2	3·26	1·5	0·4	26	—
40	61	F	0·18	141	7·3	4·5	1·3	0	15	LAD, RCA
41	57	M	0·52	75	4·9	2·45	1·0	0·9	39	RCA, LAD, Marg
42	58	F	0·72	76	4·2	2·45	1·1	0·7	29	CCA, RCA, LAD
43	39	M	0·62	55	4·8	2·2	0·7	P	13	LAD

EF, ventriculographic ejection fraction; LVEDVI, ventriculographic left ventricular end-diastolic volume index in ml/m^2 body surface area; LVED, left ventricular end-diastolic dimension in cm; LVEDI, LVED index cm/m^2 body surface area; LVPWE, left ventricular posterior wall excursion in cm; IVSE, excursion of the interventricular septum in cm; %FSLV, percentage fractional shortening of the echocardiographic left ventricular dimension; CAD, coronary artery disease; RCA, right coronary artery; LAD, left anterior descending artery; CCA, circumflex coronary artery; Marg, marginal branch of CCA; Diag, diagonal branch of the LAD; MLCA, main left coronary artery; P, paradoxical motion of the septum.

Twenty-five subjects were between the ages of 25 and 35 and the other 7 were between 45 and 50 years. There were no significant differences in the left ventricular values between the two age groups.

The upper limit of normal for the LVED in our laboratory is 5·4 cm. The LVED was increased (>5·4 cm) in 17 patients. Fifteen of these patients had an ejection fraction (EF) of 0·45 or less. Three patients had a normal LVED but an ejection fraction of <0·45. Twenty-three patients had a normal LVED and an EF of >0·45. The relation between the ventriculographic ejection fraction and the echocardiographic left ventricular end-diastolic dimension index was also determined (Fig. 2). Fifteen patients had a left ventricular end-diastolic dimension index (LVEDI) of >3 cm/m^2, all of whom had an ejection fraction of 0·45 or less. (The upper limit of normal for the LVEDI in our laboratory is 3 cm/m^2.) Three patients had a normal LVEDI and an EF <0·45. Twenty-five patients had a normal LVEDI and an EF >0·45.

The relation between the LVEDI and the ventriculographic left ventricular end diastolic volume index (LVEDVI) is shown in Fig. 3. Of the 15 patients with an LVEDI of >3 cm/m^2, 13 had a raised LVEDVI (>95 ml/m^2; the upper limit of normal for our laboratory is 95 ml/m^2). Two patients had an increased LVEDVI and a normal LVEDI. Twenty-six patients had a normal LVEDI and a normal LVEDVI.

Fig. 4 illustrates the relation between the ventriculographic ejection fraction and the echocardiographic %FSLV. The %FSLV was reduced to <28 per cent (the lower limit of normal for our laboratory is 28%) in 20 patients. In 14 of these patients the EF was ≤0·45 and in 6 the EF was >0·45. The %FSLV was normal (>28%) in 23 patients. In 2 of these the EF was <0·45%.

Abnormalities of left ventricular wall motion were frequently observed. Fourteen patients had diminished (i.e. <0·4 cm), absent, or paradoxical motion of the interventricular septum. (The lower limit of normal for displacement of the septum in our laboratory is 0·4 cm.) Thirteen of these patients had significant stenosis of the left anterior descending coronary artery (LAD). The fourteenth patient did not have coronary arteriography, but had a well-documented anteroseptal myocardial infarction in the past. On the other hand, 20 patients with significant stenosis of the LAD had septal motion which was within normal limits. Eleven patients had reduced motion (<0·9 cm) of the posterior left ventricular endocardial echo. (The lower limit of normal for our laboratory is 0·9 cm.) Six of these subjects had right coronary artery disease, 2 had disease of the circumflex coronary artery, 1 had isolated disease of the LAD, and 2 patients did not have coronary arteriography.

Examples of abnormal wall motion are illustrated in Fig. 5 and 6. Fig. 5 shows the left ventricular echocardiogram of a patient (Case 20) with normal

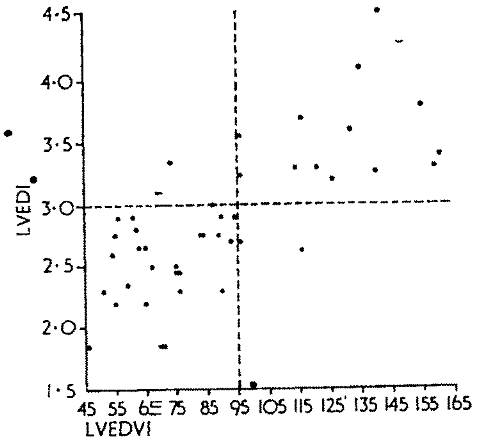

Fig. 3 *The relation between the echocardiographic left ventricular end-diastolic dimension index (LVEDI) in cm/m² and the ventriculographic end-diastolic volume index (LVEDVI) in ml/m² is shown. The horizontal dotted line shows the upper limit of normal (3 cm/m²) for the LVEDI. The vertical dotted line corresponds to the upper limit of normal for the LVEDVI (95 ml/m²). The correlation coefficient for this relation is 0·74.*

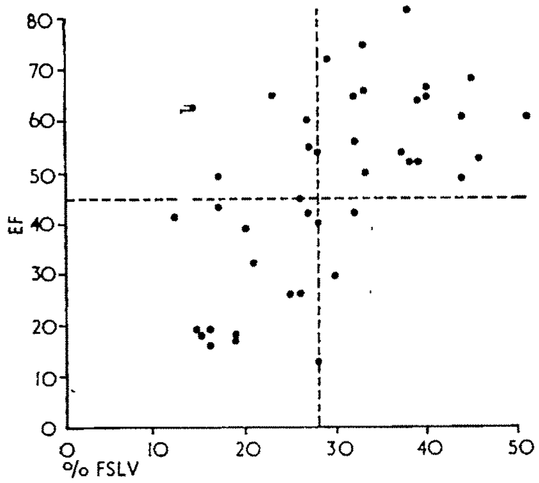

Fig. 4 *The echocardiographic percentage fractional shortening of the left ventricle (%FSLV) is plotted against the angiographic ejection fraction (EF). The horizontal dotted line corresponds to an ejection fraction of 0·45. The vertical dotted line indicates the lower limit of normal for % FSLV (28%). The correlation coefficient is 0·54.*

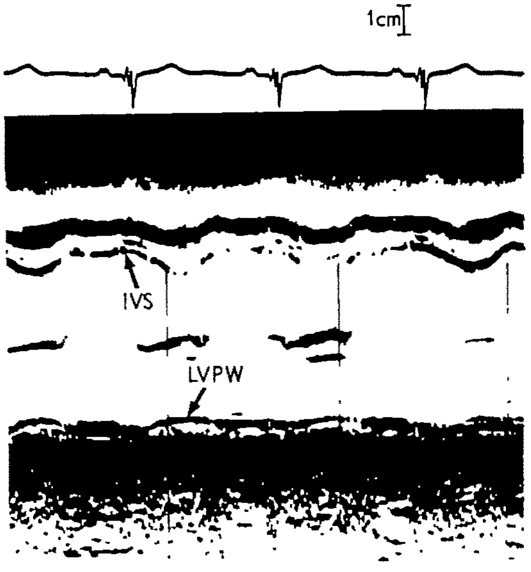

Fig. 5 *The left ventricular echocardiogram of Case 20 shows normal septal motion and much reduced motion of the left ventricular posterior wall (LVPW). IVS=interventricular septum.*

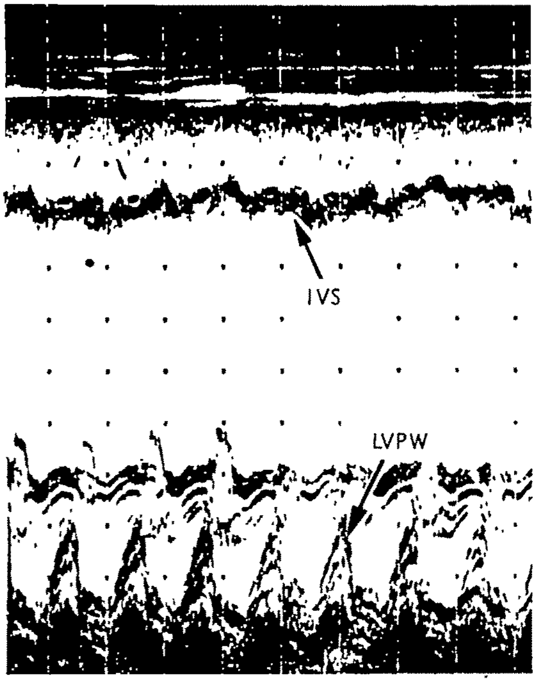

Fig. 6 *The ultrasound recording of Case 21 is shown. The left ventricle is conspicuously dilated. There is excessive motion of the left ventricular posterior wall (LVPW) to compensate for absent systolic motion of the interventricular septum (IVS), which is a thin structure.*

septal motion and pronounced reduction of posterior wall motion. The left ventricular echocardiogram of Case 21 is illustrated in Fig. 6. His ventriculographic ejection fraction was 0·17. The LVED was very enlarged (7·3 cm), with absent septal motion and there was a compensatory increase of motion of the posterior wall.

Discussion

Aortocoronary saphenous vein graft surgery is useful in the treatment of patients with angina pectoris who are refractory to medical therapy. Symptomatic relief of angina occurs in the majority of patients who have this operation (Spencer, 1970). Though the mortality for bypass surgery is relatively low in patients with good left ventricular function, the risk of surgery is considerably more for those with impaired left ventricular performance (Cohn *et al.*, 1974). Thus, the assessment of left ventricular function in these patients is of considerable prognostic importance. The left ventricular end-diastolic pressure, cardiac index, stroke work index, and the left ventricular ejection fraction have all been used as indices of left ventricular performance at cardiac catheterisation. Recent reports have indicated that the ejection fraction is the most useful index of left ventricular function in patients with coronary arterial disease (Cohn *et al.*, 1974). Patients with an ejection fraction of 0·45 or more have been considered suitable candidates for myocardial revascularisation (Committee on Coronary Artery Surgery, 1972).

In this study we used single plane ventriculograms to determine ventricular volumes and ejection fraction. We realise the limitations of this method in assessing the above values in those patients who have left ventricular asynergy. Ideally, the biplane method should be used since the single plane method tends to underestimate the ejection fraction.

The role of echocardiography in the assessment of patients with valvular and congenital heart disease has been firmly established (Zaky *et al.*, 1968; Feigenbaum, 1972; Chung *et al.*, 1973; Popp *et al.*, 1974). Recent studies have indicated the value of ultrasound in estimating the mean velocity of circumferential fibre shortening and fractional shortening of the left ventricular dimensions (McDonald *et al.*, 1972; McDonald, and Hobson, 1974; Quinones *et al.*, 1974). Echocardiography has been used to detect abnormalities of the left ventricular wall in patients with coronary arterial disease (Jacobs *et al.*, 1973; Corya *et al.*, 1974a). Klein *et al.* (1967) showed that ventricular dilatation occurred when an area of akinesis (or ventricular aneurysm) exceeded 20 to 25 per cent of ventricular surface area. Their observations were substantiated by Kitamura and co-workers (1973) who noted an increase of the end-diastolic volume and reduction of the ejection fraction when the area of the non-contractile area exceeded 20 to 30 per cent of the end-diastolic surface area of the left ventricle. Our study shows that the majority (15 of 17) of patients with an increased left ventricular end-diastolic dimension (LVED) measured by echocardiography had a critical reduction of ventriculographically determined ejection fraction (0·45 or less).

When the LVED was corrected for body surface area, all 15 patients with an increased LVEDI had an ejection fraction of 0·45 or less. Three patients with ejection fractions of 0·45 or less had left ventricular dimensions which were within normal limits. Thus an increased LVEDI was invariably associated with a critical reduction of EF, whereas a normal LVEDI did not necessarily imply an EF >0·45.

Our observations show that despite the presence of areas of asynergy an increase of the echocardiographic left ventricular end-diastolic dimension index is usually associated with an increase of the ventriculographic end-diastolic volume index. Six patients with reduced %FSLV had ejection fractions of >0·45, and 2 patients with normal %FSLV had ejection fractions of <0·45. Thus %FSLV is a less useful indicator of poor left ventricular function than the LVEDI, in patients with coronary arterial disease. This is probably because, in the presence of asynergy, %FSLV only reflects the performance of the visualised segment and not that of the entire myocardium.

Abnormalities of the left ventricular wall motion were commonly observed. Reduced motion of the interventricular septum was invariably associated with significant stenosis of the left anterior descending artery (LAD). However, several patients with significant LAD disease had normal septal motion. A compensatory increase in motion of the left ventricular posterior wall (>1·5 cm; the upper limit of normal for our laboratory is 1·5 cm) was observed in 6 patients who had absent septal motion.

In summary, our investigation indicates that enlargement of the echocardiographic left ventricular end-diastolic dimension index is usually associated with a critical reduction of the ventriculographic ejection fraction. Since patients with compromised ventricular function are not ideal candidates for aortocoronary saphenous vein graft surgery, the ability to predict a poor ejection fraction by a non-invasive method is of considerable prognostic import. We realise the limitations of a single plane echocardiogram in evaluating overall left ventricular function in coronary arterial disease. Our data indicate, however, that useful information can be gleaned from an ultrasound recording in spite of these limitations.

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Ultrastructure of abnormal membrane inclusions in nuclei of human myocardial cells[1]

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The ultrastructure of the nuclear envelope was studied in cardiac muscle cells of 12 patients undergoing cardiopulmonary bypass surgery. Two main types of membrane inclusions, globular and tubular, were observed in the nuclei. The globular type was found in 6 patients. The globular inclusions were about 0·5μ to 1·5μ in diameter and lined by two unit membranes equal in structure to that of the nuclear envelope. The lining was probably always in continuity with the nuclear membranes. Such inclusions contained a granular matrix in which no cytoplasmic organelles could be seen, with the exception of a limited number of ribosomes. The tubular type of nuclear inclusion was observed in the cardiac tissue of 3 patients. These tubules ran in straight or slightly bent segments of about 0·2μ to 1·6μ length, interrupted by bendings at obtuse or right angles. The diameter of their lumina measured about 300 Å to 800 Å. Such tubules were nearly always found in areas of the nucleoplasm rich in heterochromatin. Nuclear pore-like structures were occasionally found in the tubular wall. The tubular wall consisted of a single unit membrane shown to be in continuity with the inner membrane of the nuclear envelope. Since these nuclear aberrances have been observed at all of the stages examined, the possibility is considered that they may represent a specific nuclear response to the process of cardiac hypertrophy.

Additional information concerning the mechanism of cardiac enlargement may be gained by studying the ultrastructure of the nuclei of hypertrophied myocardial cells. In a recent publication, Ferrans *et al.* (1975) showed the presence of abnormal membrane inclusions in nuclei of human myocardial cells. Similar findings have been reported in cell nuclei of a variety of cells (Bernhard and Granboulan, 1963; Clyman, 1963; Terzakis, 1965; Babai *et al.*, 1969). In an ultrastructural study of the hypertrophied human myocardium (Jensen *et al.*, 1976; Saetersdal *et al.*, 1976) we have observed intranuclear membrane structures similar in general appearance to those reported by Ferrans *et al.* (1975). Our findings, however, vary to a certain extent from those presented in the latter paper. Furthermore, the biopsies of the present study, being taken at three different stages during open heart surgery, allow for a comparison between the presence of nucleic aberrations and the state of ischaemia of the heart wall during cardiopulmonary bypass.

Subjects and methods

The present observations were made in a group of 12 patients undergoing cardiopulmonary bypass surgery because of congenital septal defect and congenital or acquired valvular disease. In 8 patients examinations were performed on three biopsies from each patient, i.e. at the start and end of aortic crossclamping and after 20 minutes of reperfusion. In 4 patients biopsy was only taken at the start of cardiopulmonary bypass. Biopsies were obtained from the left ventricular wall by the Vim Silverman technique (Rake *et al.*, 1969) using a Tru-Cut biopsy needle (Travenol Laboratories, Inc., Deerfield, Ill. 60015, USA). The anoxic period varied between 30 and 78 minutes during which the heart was protected by local cardiac hypothermia (15°C).

Specimens were fixed for 3 hours in an ice-cold solution of Karnovsky's fixative (1965) to which 5 per cent sucrose was added. The tissue was washed overnight in a cacodylate-buffered 1 per

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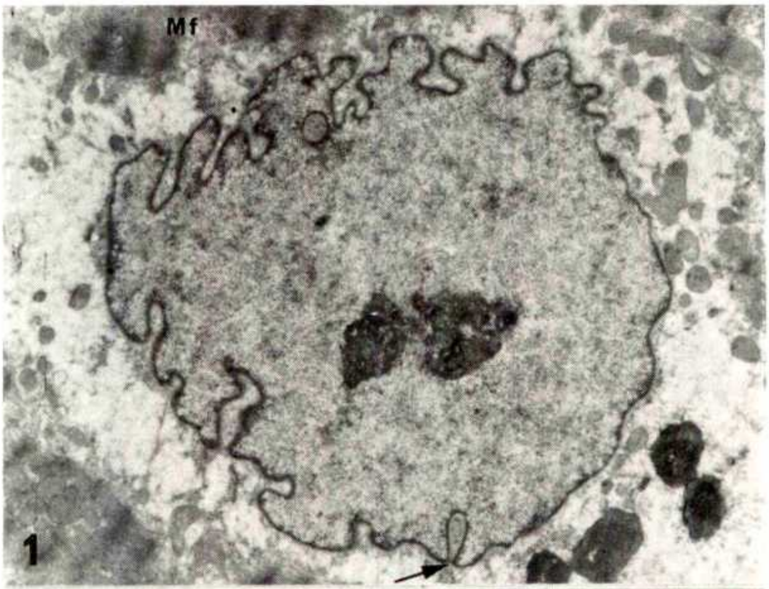
cent sucrose solution before being treated with 1 per cent cacodylate-buffered OsO_4 solution for 1½ hours. Then, after a wash in the same buffer and a wash in distilled water, the tissue was stained *en bloc* for 1½ hours in a 2 per cent uranyl acetate solution before being dehydrated through an



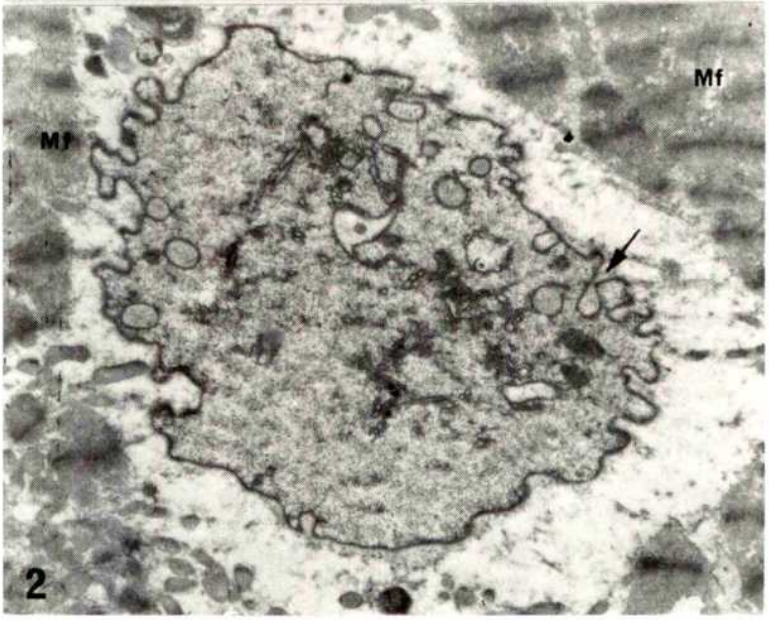


Fig. 1 *Myocardial cell nucleus of a 52-year-old patient with aortic valvular stenosis. The lateral surfaces of the nucleus show serrated contraction folds. Two pseudoinclusions are present, one at upper left and another at arrow. The lumen of the latter can be seen to be in continuity with perinuclear area. Mf = Myofilaments. (× 6150.)*

Fig. 2 *Myocardial cell nucleus of a 52-year-old patient with aortic valvular stenosis. Nucleus shows both types of inclusions, globular and tubular, in the nucleoplasm. Globular inclusions are mostly confined to the peripheral parts and are probably always in continuity with the nuclear envelope (arrow). The small sized tubular inclusions are particularly abundant in the heterochromatin-rich areas of the nucleoplasm. Mf = Myofilaments. (× 6400.)*

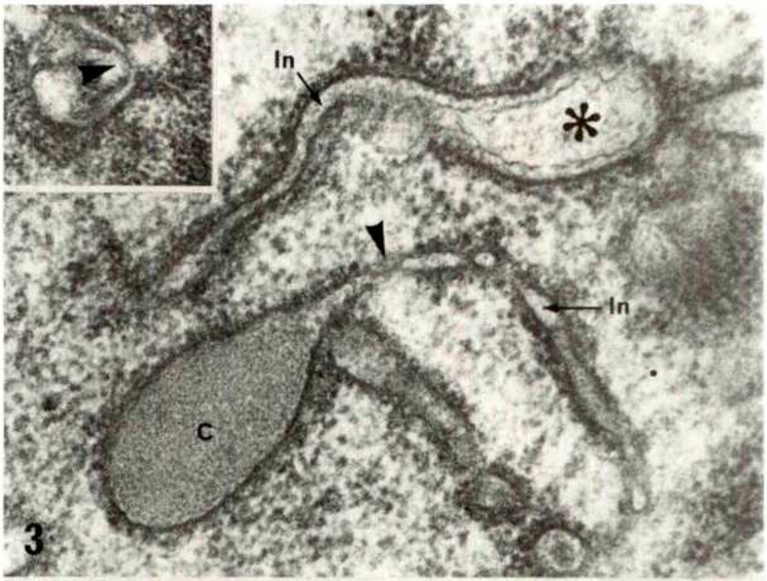


Fig. 3 *Part of a myocardial cell nucleus of a 52-year-old patient with aortic valvular stenosis. The micrograph shows intranuclear tubles (In) marginated by heterochromatin. The tubule at the upper left is in continuity with a pseudoinclusion (asterisk), showing that the single-membraned wall is in continuity with the inner nuclear membrane. The tubular dilatation (C) is filled with a granular material. A nuclear pore-like structure is present at arrowhead. Inset shows a segment of a curved tubule with a nuclear pore-like structure at arrowhead. (× 54820.) [Inset: × 33770.]*

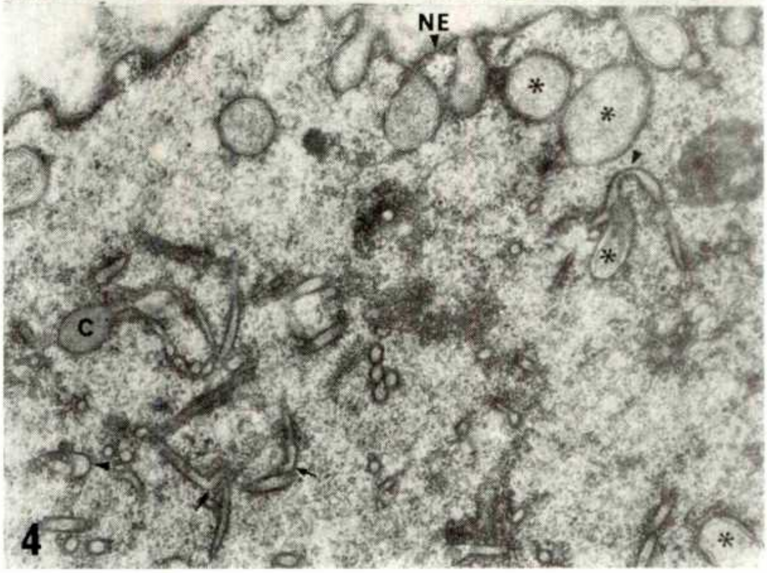


Fig. 4 *Part of a myocardial cell nucleus of a 52-year-old patient with aortic valvular stenosis. The nucleoplasm contains numerous cylindrical and small sized tubules surrounded by heterochromatin. These tubules may run singly, or a few tubules may have their walls closely applied to each other (transversely cut tubules in the centre of the micrograph). Straight or slightly bent segments of the tubules are interrupted by bendings at obtuse or right angles (arrows). Also, curved tubules can be seen (arrowheads). Asterisks = pseudoinclusions, C = tubular cistern; NE = nuclear envelope. (× 16500.)*

ethanol series. The ultrathin sections were grid-stained with lead citrate (Reynolds, 1963).

Results

The nuclear membranes of myocardial cells showed serrated folds caused by the state of contraction (Fig. 1). In addition, the nuclear envelope displayed pseudoinclusions (Fig. 1, 2, 3, and 4) which appeared oval or circular in sections and were not related to cellular contraction. Such structures were mostly confined to the peripheral parts of the nucleus. The membranes of these inclusions were shown to be continuous with those of the nuclear envelope. Yet, probably depending on the plane of sectioning, most of the pseudoinclusions appeared isolated in the nucleoplasm with no visible continuity with the nuclear membranes. The infoldings were lined by both of the membranes of the nuclear envelope and by an outer covering of heterochromatin (Fig. 4). Nuclear pores occurred in these membranes at a seemingly normal frequency. The pseudoinclusions measured about 0·5μ to 1·5μ in diameter and contained a granular matrix. Though the latter was occasionally seen to contain ribosomes, other cytoplasmic organelles were not observed in this area. Aberrances of the nuclear envelope, as described above, were noted in 6 of 12 patients and in all three stages examined.

In addition, in 3 of 12 patients, approximately 2 to 3 per cent of the total number of nuclei studied contained cylindrical and small-sized tubules within their nucleoplasm (Fig. 2 to 7). These were lined by a single cell membrane only, shown to be continuous with the inner membrane of the nuclear envelope (Fig. 3). Such tubules mainly occurred in areas of the nucleus rich in heterochromatin. The actual number of intranuclear tubules, as recorded in one single section, varied greatly. While in some nuclei they were only few in number, in others, numerous short and almost straight tubules emanated through the nucleoplasm in different directions (Fig. 4, 7).

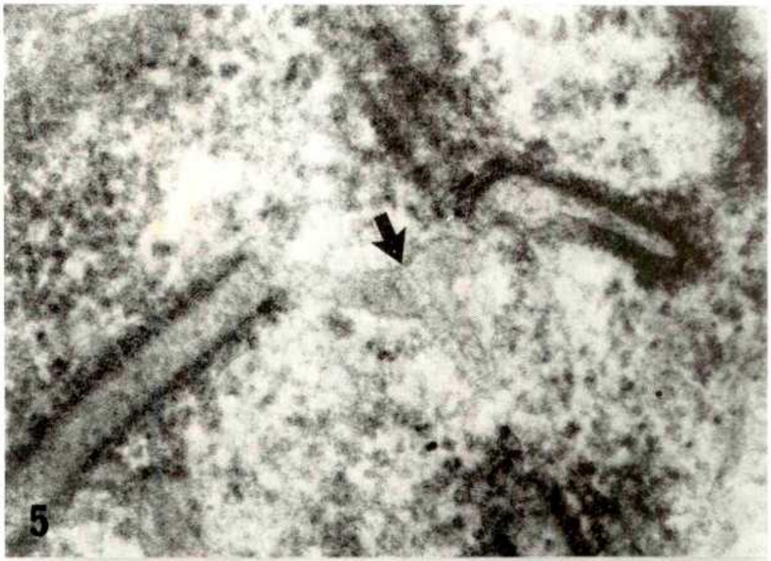
Comparisons between different planes of sectioning showed that the intranuclear tubules may run singly, or a few tubules may have their walls so closely applied (Fig. 4) as to appear as bundles in the nucleoplasm. Occasionally, each tubule could be seen to be surrounded by a separate sheath of chromatin of about 160Å to 200Å thickness. More frequently, however, the tubules were enclosed in aggregations of heterochromatin of various densities and extensions (Fig. 2, 6, and 7). These aggregations were continuous with the submembraneous heterochromatin of the nucleus (Fig. 6) and measured about 0·4μ to 2·0μ in diameter. The intranuclear tubules ran in straight or slightly bent segments of about 0·2μ to 1·6μ length, interrupted by bendings at obtuse or right angles (Fig. 4). Now and then, segments of curved tubules were also observed. Tubules not associated with chromatin, and with a clear lumen, were seen in continuity with the former ones (Fig. 5). Such tubules had an irregular course and could be seen to form coiled aggregates (Fig. 7).

The diameter of the tubular lumen measured from 300Å to 800Å. It was sometimes seen to be continuous with dilated circular sacs filled with a finely granular material (Fig. 3, 4 and 7). A similar material, consisting of somewhat larger granules of moderate electron density, was also found within the tubules (Fig. 5). A rare observation was the presence of nuclear pore-like structures formed by the tubular walls (Fig. 3). In such instances, the apposing membranes of the tubule occluded the lumen for approximately 700Å′ length. The marginating chromatin was absent at both sides of the pore-like structure. A close association between the nucleolar material and the intranuclear tubules could not be detected in the present material. In one instance, an aggregation of coiled tubules was seen to be enclosed in electron dense material which appeared similar to the heterochromatin (Fig. 6).

Intranuclear tubules, as described above, were seen in cardiac tissues of 3 patients. In 2 of these, globular infoldings of the nuclear envelope also occurred. These two aberrances of nuclear membranes were often encountered in the same areas of the nucleoplasm. Of the 2 patients mentioned above, one (aged 52 years) with aortic valvular stenosis, had severe hypertrophy of the left ventricular wall. In the other patient (aged 60 years), with aortic valvular regurgitation and mitral valvular stenosis resulting from rheumatic disease, only a light hypertrophy of the left ventricular wall was found. The latter also applied to the third patient (aged 4 years), with congenital ventricular septal defect and pulmonary valvular and infundibular stenosis. In the first and second patient mentioned above, intranuclear tubules were found to be present at all of the three stages examined, i.e. at the start and end of aortic cross-clamping and after 20 minutes of reperfusion. In the third patient, biopsy was only taken at the start of cardiopulmonary bypass.

Discussion

The present study reports two main types of inclusions, globular and tubular, in nuclei of



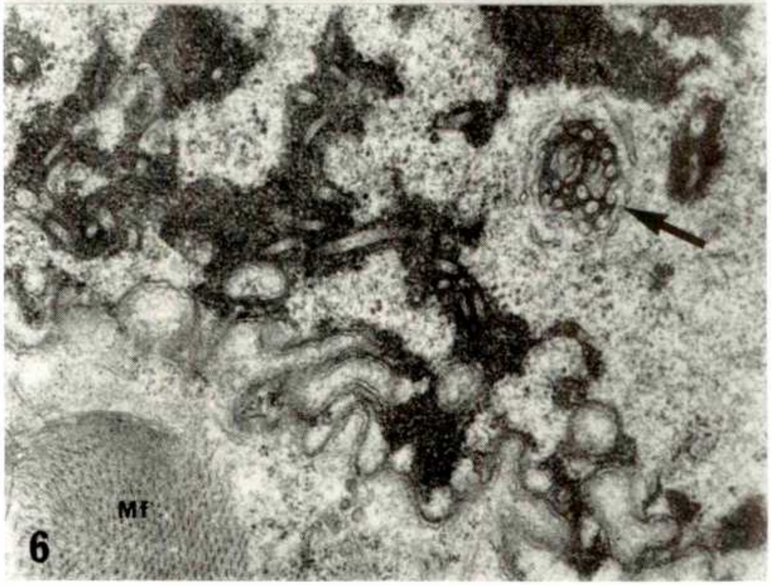


Fig. 5 *Part of a myocardial cell nucleus of a 52-year-old patient with aortic valvular stenosis. Intranuclear tubules are presented at a large magnification showing the granular matrix of the tubular lumen and the marginated heterochromatin. A tubule not associated with chromatin (arrow) is continuous with the chromatin-invested one. (×77300.)*

Fig. 6 *Part of a myocardial cell nucleus of a 60-year-old patient with aortic valvular regurgitation and mitral valvular stenosis caused by rheumatic disease. Intranuclear tubules are 'embedded' in dense condensations of heterochromatin. In addition, segments of a coiled tubule (at arrow) appear closely invested by chromatin-like material. Mf=Myofilaments. (×27870.)*

human myocardial cells. The globular type of inclusion was lined by a double membrane and superficially located in the nucleus. Such structures were originally described by Bernhard and Granboulan (1963) in cancer cell nuclei and named 'pseudoinclusions'. They have since been found in cell nuclei of a variety of cells (Babai *et al.*, 1969; Sobel *et al.*, 1969; Ferrans *et al.*, 1975).

The pseudoinclusions of the present study are probably always in continuity with the nuclear

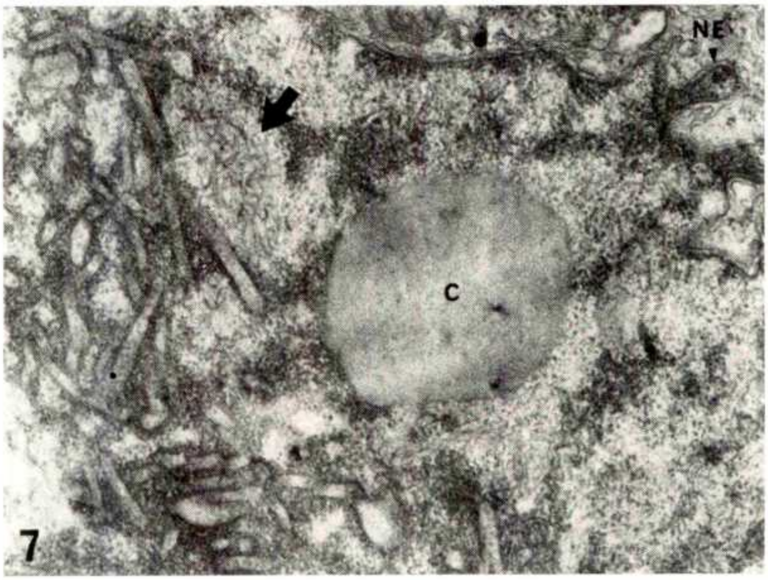


Fig. 7 *Part of a myocardial cell nucleus of a 4-year-old patient with congenital ventricular septal defect and pulmonary valvular and infundibular stenosis. In addition to a large number of straight running tubules embedded in heterochromatin, a mass of coiled tubules is present at arrow. C = tubular cistern; NE = nuclear envelope. (× 27700.)*

envelope even though they often lie seemingly isolated in the submembraneous area. The origin of their lining from the nuclear envelope is evident, though, since it consists of two unit membranes (marginated by heterochromatin), with nuclear pores present at a normal frequency. The functional significance of these nuclear aberrances is still unknown. Previous studies (Babai *et al.*, 1969; Ferrans *et al.*, 1975) have reported that the pseudoinclusions contain cytoplasmic organelles normally present in the perinuclear area. Such cytoplasmic organelles were seen by us only in the larger cytoplasmic invaginations of the nuclear envelope. In our opinion, however, these invaginations are basically different from the globular pseudoinclusions. In the latter, a granular matrix occurred similar to the surrounding chromatin and with no cellular organelles present other than a limited number of ribosomes. Hence, our observations might suggest a functional significance of these nucleic aberrances other than a mere 'trapping' of perinuclear cytoplasm.

Nuclear inclusions which have been previously described show structural similarities to the second type of inclusions reported in the present paper. These are tubular structures lined by a single membrane. In human endometrial cell nuclei (Clyman, 1963; Ancla and DeBrux, 1965; Terzakis, 1965), ringshaped and tubular structures have been shown to be closely connected with the nucleolus, and, also in continuity with the perinuclear space. In the nuclei of an intercranial sarcoma cell, a Golgi-like structure has been reported (Bucciarelli, 1966) in continuity with the inner nuclear membrane. In a recent report, Ferrans *et al.* (1975) showed the presence of intranuclear tubules derived from the inner nuclear membrane in human cardiac muscle cells. In addition, intranuclear tubules of various configurations have been reported to occur as the result of cardiac viral infections (Middelkamp *et al.*, 1967; Patrizi *et al.*, 1967).

It appears from the present study that intranuclear tubules, similar to those reported above, nearly always are found in areas of the nucleoplasm rich in heterochromatin. Yet, the tubules are not merely channels in the chromatin. The presence of a trilaminar unit membrane encircling the tubular lumen is evident. This is particularly clear in areas where the chromatin invested tubules are continuous with tubules not surrounded by chromatin (Fig. 5).

The often dense packing of tubules at varying sizes, and their close proximity to the heterochromatin seems to be a characteristic feature. In considering their mode of formation, therefore, the possibility cannot be entirely excluded that the tubules arise by the synthesis of membranes within the nucleoplasm. Such a view, however, is hardly favoured by two of the present observations, namely the continuity between the tubular membrane and the inner nuclear membrane, and, by the presence of nuclear pores in the tubular wall (Fig. 3). With regard to the latter, is it well known that in rapidly dividing cells, such as malignant cells and öocytes, nuclear pore-like structures do occur in 'annulate lamellae' of the endoplasmic reticulum. These are considered as complicated foldings of the nuclear envelope. To our knowledge, nuclear pore-like structures have not previously been reported in intranuclear tubules derived from the inner nuclear membrane.

The straight or slightly bent intranuclear tubules presented by us, are structurally in accord with those described by Babai *et al.* (1969) in Novikoff hepatoma cells and by Ferrans *et al.* (1975) as 'tubules of the first type' in human cardiac muscle cells. Yet, a significant observation of the present study, not reported in earlier works, is the presence of pronounced tubular bendings at the points of termination of the straight running segments.

In addition, the coiled tubules occasionally observed by us in the nucleoplasm, show similarities to those described by Ferrans *et al.* (1975) as, 'tubules of the second type'. But, in our study such tubules can also be seen to be surrounded by electron dense and chromatin-like material (Fig. 6). Still another significant observation was that pseudoinclusions and intranuclear inclusions were often encountered within the same areas of the nucleoplasm. This might suggest either a common course of formation, or, a functional relation between the two types of membrane aberrances.

Nuclear abnormalities, as described above, were never seen by us in normal mammalian myocardium. They could hardly be caused by cardiac viral infection since viral particles were never seen in the tissues. Both types of inclusions were found at all of the stages examined in the present study. Accordingly, they could not be a reaction to the ischaemia of the heart wall. The alternative, therefore, should be considered that the nuclear aberrances reported might represent a specific response to the process of cardiac hypertrophy (Ferrans *et al.*, 1975).

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Learned voluntary control of heart rate and rhythm in two subjects with premature ventricular contractions[1]

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Two people with frequent premature ventricular contractions and bigeminal rhythm not associated with other signs of heart disease, learned to suppress the arrhythmia using a biofeedback technique. In both cases, physical exercise and atropine suppressed the arrhythmia, and in both the learned control was related to the development of tachycardia. In Case 1, it appeared to depend on something more than speeding alone, for sinus rhythm could be maintained during voluntary control at a lower heart rate than during physical manoeuvres such as exercise. In Case 2, the premature ventricular contractions could be induced by a sudden fall of heart rate, e.g. after a Valsalva manoeuvre, and could be suppressed by voluntary increase of heart rate by up to 40 beats/minute produced with little change in breathing or muscle activity.

The treatment of premature ventricular contractions in a patient with an otherwise normal heart is often very unsatisfactory. If the premature ventricular contractions are troublesome enough to warrant treatment, the decision to use antiarrhythmic drugs is influenced by the fact that not only are the drugs often ineffective, but also dangerous. Nearly all the drugs in common use for this purpose act directly on the heart, but there is increasing evidence, reviewed by Mauck and Hockman (1967), that the central nervous system may influence the appearance and disappearance of premature ventricular contractions. Recent work (Lown *et al.*, 1973a; Pickering *et al.*, 1976) has shown that the frequency of these contractions often falls during sleep, and, conversely, that ventricular tachyarrhythmias may be precipitated by psychological stress (Lown *et al.*, 1973b).

One possible alternative mode of treatment has been proposed by Weiss and Engel (1971), who found that some patients with frequent premature ventricular contractions were able to learn to control them voluntarily. The training consisted of learning to produce small changes of heart rate in both directions, using a biofeedback technique where a yellow light signalled the correct response. In 5 out of 8 patients, the acquisition of this ability was found to be associated with a decreased frequency of premature ventricular contractions, which appeared to be maintained outside the laboratory situation. The present work, a preliminary report of which has already been published (Pickering and Miller, 1975), was undertaken to examine further the possibility of direct voluntary control of premature ventricular contractions, and to investigate the mechanisms of such control. Two patients were studied, who will be described separately because there were considerable differences both in the manifestations of the contractions and in the type of training used.

Case 1

PREVIOUS HISTORY

A 14-year-old boy who had always been in good health and free of any cardiac symptoms, was noted to have an irregular pulse $2\frac{1}{2}$ years previously on a routine medical examination, but no other abnormality was found. The electrocardiogram showed frequent premature ventricular contractions: because these often occurred in runs of three or more, it had been decided that they should be treated. At rest, however, the rhythm was usually bigeminal, interspersed with brief runs of sinus rhythm. For various reasons, treatments with lignocaine, quinidine, or propranolol were all unsuccessful. Pharmacological tests were carried out at the University of Pennsylvania Medical School by Dr. T. Weiss. These showed that intravenous phenylephrine, phentolamine, propranolol, edrophonium, lignocaine, and isoprenaline all failed to suppress the

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premature ventricular contractions. Particularly noteworthy is the fact that with isoprenaline they persisted unchanged up to a heart rate of 143/minute. Only atropine abolished them, above a rate of 110/minute.

He had no symptoms directly attributable to his arrhythmia and was unable to tell whether he was in sinus or bigeminal rhythm.

METHODS AND PROCEDURE

The principal aim of the training procedure was to enable the patient to develop voluntary control over his heart rate or rhythm. Since he was not normally aware of either, an appropriate change of the variable to be controlled was signalled to him as soon as it occurred. Learning a physical skill (such as heart rate control, or riding a bicycle) is often largely a matter of trial and error. While knowledge of results (success or failure) is essential for learning to take place, it is not necessary to know exactly how or why the correct response is produced. One cannot learn to ride a bicycle simply by reading a book about it. Thus, no particular instructions could be given as to how the patient should succeed, but verbal encouragement was given whenever there was a change in the required direction. To begin with, such changes are largely spontaneous, but later one can be produced voluntarily. Heart rate training was initially tried using a method similar to the one described by Weiss and Engel (1971), but because the subject was in bigeminal rhythm most of the time while at rest, this proved unsatisfactory, and it was found easier to give the feedback in the form of the electrocardiographic trace displayed on the oscilloscope screen of a cardiac monitor. With the electrode configuration used, the difference between the sinus beats and the premature ventricular contractions was obvious.

Training was continued over a period of 6 months. A total of 115 'trials' (defined below) was performed, and there were usually 4 trials per session. At the beginning of each session, four standard procedures were carried out. These were: (a) Valsalva's manoeuvre, straining at 40 mmHg for 10 seconds, (b) hyperventilation for 45 seconds, (c) breath-holding for 45 seconds, and (d) isometric hand grip for 45 seconds.

Respiration was recorded by a pneumograph round the chest connected to a low-pressure transducer. Palmar galvanic skin conductance was also recorded. Records were taken on an 8-channel Grass polygraph. The training procedure was done with the subject lying supine on a bed, facing the oscilloscope screen. The recording apparatus was in an adjoining room out of sight of the subject. The control periods (4 minutes) were done with the oscilloscope screen disconnected, and the subject lying at rest. During the training periods, or trials (usually 13 minutes), he watched the screen and was instructed to maintain a pattern of normal rhythm for as much time as he could. He was told that it would be better if he did this without changing his breathing or tensing his muscles, but no particular emphasis was placed on this. Some trials without feedback were done with the oscilloscope disconnected. His ability to detect changes of rhythm was tested at intervals by asking him to press a button (which produced a mark on the paper record) every time he thought his rhythm had changed from sinus to bigeminal and vice versa. He was never able to do this consistently.

The results were analysed by classifying the rhythm as sinus, bigeminy, or trigeminy, and expressed as the percentage of time in each rhythm during each control or trial period.

Results

EFFECTS OF PHYSICAL MANOEUVRES ON RHYTHM

While resting on the bed between the four standard procedures, he was normally in bigeminal rhythm. Hyperventilation, isometric hand grip, and Valsalva manoeuvres tended to produce runs of sinus rhythm, following an increase in the sinus rate. Dynamic bicycle exercise was also carried out on two occasions. On the first (three weeks after the start of training), the premature ventricular contractions were suppressed above a sinus rate of 156/minute. On the second (after 10 weeks of training), the contractions disappeared above a rate of 129/minute.

LEARNED CHANGES OF RHYTHM

13-minute trials

An ability to increase the amount of sinus rhythm was not at first apparent and was only acquired after trial 9. Before this trial, there was no significant difference between the amount of sinus rhythm during the control periods (mean 2·9%) and the trial periods (mean 5·2%), but after trial 10, a consistent difference between the two was apparent. Thus, for the next 9 trials, sinus rhythm was present for 6·2 per cent of the control time and 32·7 per cent of the trial time, and this difference was significant ($t=5{\cdot}01$, $P<0{\cdot}001$). Comparison of the first 10 trials of training with the last 10 (done 6 months later), showed that during the first 10 sinus rhythm was present 5·3 per cent of the time during rest, and 8·7 per cent during training, a difference of only 3·4 per cent. For the last 10 trials, the percentage of time in sinus rhythm was

3·2 per cent at rest and 27·4 per cent during the trial periods, a difference of 24·2 per cent. He thus showed the development of voluntary control of his rhythm over a period of several months. He was not able to maintain a significant increase of sinus rhythm during 'no-feedback trials' (when the oscilloscope was disconnected).

2-minute trials
During these trials, the subject was asked to switch alternately from one rhythm to the other every two minutes. An example of such a trial is shown in Fig. 1, which is a continual strip of electrocardiogram in 2-minute segments. The subject attempted to change his rhythm at the beginning of each segment. While he is at rest (R in the Fig.), there is bigeminal rhythm. During the periods marked S (attempting to maintain sinus rhythm), there are periods of sinus rhythm which revert to bigeminy during the alternate periods (B, when he was attempting to maintain bigeminal rhythm). One noteworthy feature is that the galvanic skin conductance showed consistent changes between the two types of rhythm. During the periods of bigeminal rhythm, the skin conductance was low, whereas the beginning of each period of sinus rhythm was accompanied by an increased skin conductance, indicating sympathetic arousal. The pattern of breathing tended to be different also; during the periods of sinus rhythm it became faster and more irregular.

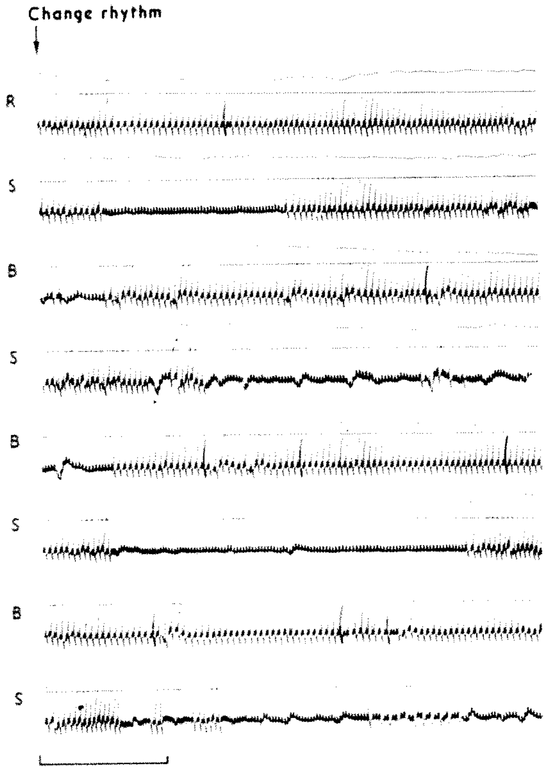

Fig. 1 *Case 1. Continuous 16-minute record (in 2-minute segments) of electrocardiogram and skin conductance (upper line of each trace). R = Rest. Change rhythm = instruction to change rhythm either to sinus (S) or bigeminy (B) for two minutes. Premature ventricular contractions have a large amplitude on the electrocardiogram; sinus beats are small. Note increase of conductance following S, but not B.*

CHANGES OF RATE DURING CHANGES OF RHYTHM

Since the transition from bigeminal rhythm to sinus rhythm during the physical procedures was associated with a relative tachycardia, it was of interest to know whether the same was true of the learned rhythm changes. Analysis of the voluntarily produced transition from bigeminal to sinus rhythm showed that there was a consistent speeding from an average sinus rate of 90·6/minute at the end of bigeminal rhythm to 95·6/minute at the onset of sinus rhythm.

Once sinus rhythm had been achieved, however, this speeding did not appear to be maintained. The relation between heart rate and rhythm, both for the 'physical manoeuvres' described above, and for the training periods was analysed by the following method. The average sinus rates for all periods of sinus or bigeminal rhythm lasting more than 10 seconds were measured. For the physical manoeuvres, measurements were made both while the subject was at rest on the bed and while performing the various manoeuvres. Periods of intermediate rhythm, e.g. trigeminal, were excluded from this analysis. The results were plotted as histograms showing the relative prevalence of the two rhythms (sinus and bigeminal) at different heart rates. The upper part of Fig. 2 shows that during the various physical manoeuvres, sinus rhythm prevailed at higher rates, and bigeminal rhythm at lower rates.

When the data for the training periods were analysed in the same way (lower half of Fig. 2), the results were very different. The distribution of bigeminal rhythm in relation to heart rate was much the same as for the physical manoeuvres, but most of the sinus rhythm now occurred at lower heart rates than those during bigeminal rhythm. This means that the learned, voluntarily produced sinus rhythm was not simply the result of maintained speeding of the heart, as was the case with the physical manoeuvres. During the voluntarily

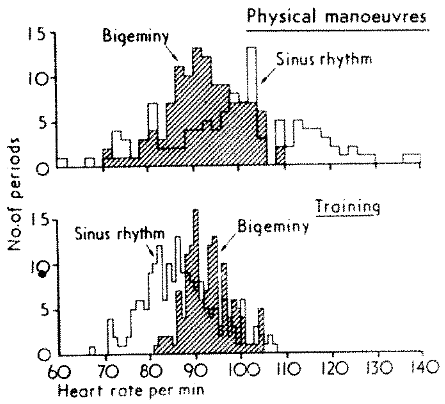

Fig. 2 *Case 1. Relative prevalence of bigeminal (hatched) and sinus rhythms at different heart rates. Each period = one episode of at least 10 seconds' duration. Top panel: during physical manoeuvres; Lower panel: during trials. See text for descriptions.*

produced sinus rhythm, the initial speeding associated with the change from bigeminy to sinus rhythm was followed by a period of slowing without the reappearance of bigeminal rhythm.

Case 2

PREVIOUS HISTORY

The second patient was a 35-year-old man who for one year before the study had experienced episodes of palpitation lasting for several hours at a time, which were uncomfortable and brought on feelings of fatigue and helplessness. At first, he would lie still until they eventually passed off, but found that physical exercise would sometimes suppress them.

Physical examination and the electrocardiogram showed no abnormality other than premature ventricular contractions. Most of the time these were sporadic, but during symptomatic attacks, the rhythm was bigeminal.

METHODS AND PROCEDURE

The recording procedure was the same as for Case 1, except that feedback was given in the form of a meter connected to the output channel of the Grass cardiotachograph, which was directly calibrated in beats per minute. Since the arrhythmia was more intermittent than in the first case, emphasis was placed on being able to produce short bursts of speeding, and the trials were normally for 30 seconds each.

The ability to detect premature ventricular contractions and the effects of physical manoeuvres on the arrhythmia were tested as in Case 1.

He was seen on two separate occasions 5 months apart. On each occasion, he attended for 4 days at a time and performed 4 training sessions a day, of about an hour each.

Results

EFFECTS OF PHYSICAL MANOEUVRES ON RHYTHM

While at rest on the bed, he was in sinus rhythm most of the time with sporadic premature ventricular contractions. His ability to detect these was tested as for the first subject; 10 per cent of 32 sporadic premature ventricular contractions were correctly detected, but he gave 12 false positive signals. The onset of bigeminal rhythm was always correctly identified.

Valsalva manoeuvres nearly always induced the bigeminal rhythm during the overshoot phase of the manoeuvre when there was a period of intense reflex bradycardia. The other three standard procedures did not induce the arrhythmia. Exercise on the bicycle ergometer reduced the frequency of premature ventricular contractions, which were absent above a rate of 115/minute.

LEARNED CHANGES OF RATE AND RHYTHM: FIRST VISIT

When first tested, he could produce no consistent tachycardia, but by the end of the first visit (16 sessions), he could increase his rate by 20 to 25/minute. During the speeding trials, there was at first a noticeable change in the respiratory pattern and in the activity of the EMG of the chin muscles. As with the first subject, palmar skin resistance decreased. The tachycardia was usually accompanied by a rise of diastolic pressure. The speeding was usually maintained for only 30 seconds, but he was able to maintain a heart rate increase of 10/minute or more for 8 minutes.

SUPPRESSION OF PREMATURE VENTRICULAR CONTRACTIONS

Once the ability to speed the heart voluntarily had been acquired, he was able to learn to suppress the bigeminal rhythm, which was first brought on by performing a Valsalva manoeuvre. A typical episode is shown in Fig. 3, which is a polygraph record of muscle tension (EMG) from the chin, heart rate, electrocardiogram, and respiration during two attempts to suppress the arrhythmia. It will be noticed that the first attempt shown here was unsuccessful, but the second suppressed the arrhythmia. The average sinus rate at the transition point to sinus rhythm was 117 ± 8/minute. One frequent finding at this stage can be seen in Fig. 3; he often needed two attempts to suppress the premature ventricular contractions but, as shown in the figure, the rate at which the transition finally occurred during the second attempt was usually lower (116±8/minute) than the maximum rate achieved during the first (123±7/minute); this difference was significant ($t=4\cdot39$, $P<0\cdot002$).

During 20 attempted suppressions of the arrhythmia, bigeminal rhythm was present for a total of 2304 seconds while he was at rest, and it stopped spontaneously only once (a few seconds after an attempted suppression). He was trying to suppress it for a total of 639 seconds, during which time it stopped 19 times. This difference was significant ($\chi^2=64\cdot0$, $P<0\cdot005$). He was able to do this with or without feedback, though he was unable to tell exactly when sinus rhythm was resumed unless feedback was present.

SUBSEQUENT PROGRESS

During the following two months, he was able to suppress the bigeminal rhythm on about 50 per cent of occasions. He bought himself a cardiac monitor and practised heart-rate speeding at home. He noticed that it was harder to suppress the arrhythmia when it came on spontaneously than when he induced it himself.

SECOND VISIT

He could now increase his heart rate by 20 to 40/minute equally well with or without feedback. With the feedback on, he was able to hold his rate very accurately at any given level between 70 and 110/minute (Fig. 4). This figure shows that EMG and respiratory changes were more pronounced at the higher heart rates, and also that sporadic premature ventricular contractions were more likely to occur during a period of rapid slowing (as seen earlier during the Valsalva manoeuvre) than at any steady level of heart rate.

He was now able to maintain sizeable increases of rate (about 20/minute) without any noticeable change in his breathing or chin EMG activity (Fig. 5). In the example shown in this figure, he increased his rate from 76 to 95/minute. He could also speed his heart while holding his breath. Although the skeletal changes (i.e. breathing and EMG) could be eliminated, the associated autonomic changes, i.e. rise of skin conductance and diastolic pressure (in this instance by 10 mmHg) persisted.

Valsalva manoeuvres were again used to induce the bigeminal rhythm. This time he was even more successful at suppressing the arrhythmia. In 10 trials the arrhythmia did not stop at all during 1603 seconds while he was resting, but stopped 10/10 times during 112 seconds while he was trying to

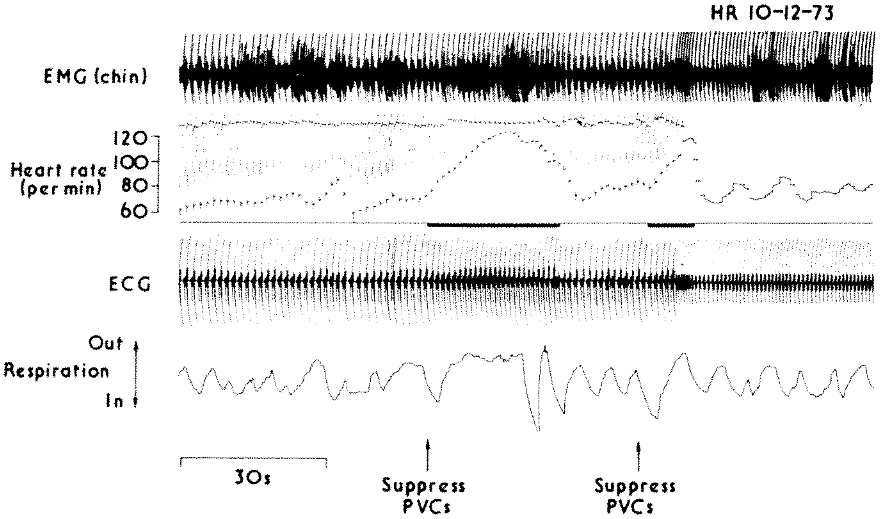

Fig. 3 *Case 2. Voluntary suppression of premature ventricular contractions. Upper trace = chin EMG (with electrocardiograph artefact). Second trace = heart rate: early part of record is bigeminal rhythm, and irregularity is caused by premature beats followed by compensatory pause. Solid bars = subject presses buzzer to indicate attempted suppression, which succeeds on second attempt.*

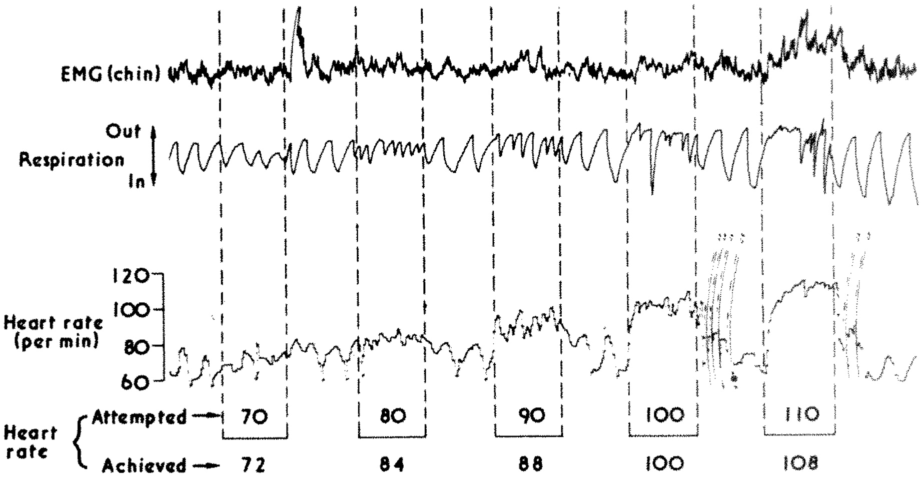

Fig. 4 *Case 2. 30-second alternations of rest and speeding to different rates. Achieved = actual rate over last 15 seconds. Note increasing EMG and respiratory changes at higher rates and onset of premature ventricular contractions following the last two speeding episodes (large deflections on heart rate record).*

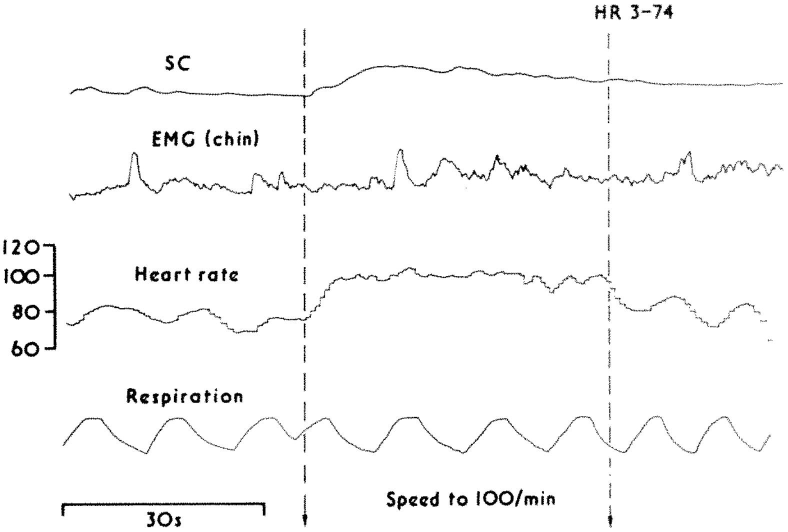

Fig. 5 *Case 2. Ability to speed heart in absence of respiratory or EMG change, but change of skin conductance (SC) persists.*

suppress it. This difference was significant ($\chi^2 = 132{\cdot}9$, $P < 0{\cdot}005$). He was successful on the first attempt on 9 out of the 10 trials.

EFFECT OF ATROPINE

Fig. 6 shows the effect of 2·8 mg atropine on the voluntary tachycardia. Before it was given, he was able to produce brief 5-second bursts of acceleration having almost a square wave appearance on the heart rate trace. The rapidity of these changes suggests that they were most likely mediated vagally. After administration of atropine, the heart rate rose to 120/minute. Despite this, he was still able to produce small and brief periods of acceleration (of 15/minute), but their appearance was now quite different (right hand panel of Fig. 6). The peak acceleration was now not reached until after he had stopped trying to produce it, and took many seconds to decay. This pattern is consistent with a sympathetically mediated change. Valsalva manoeuvres no longer produced premature ventricular contractions, and none was seen in the hour following the atropine.

Discussion

The chief finding of these investigations is that learned voluntary control of premature ventricular contractions can be achieved, confirming the findings of Weiss and Engel (1971). The two cases described here were similar in that both occurred in young people with otherwise normal hearts, and in both the appearance and disappearance of the arrhythmia were strongly influenced by changes of heart rate. Thus in both cases, the voluntary production of sinus rhythm was preceded by an increase in the sinus rate during bigeminy. In the first case, the sinus rhythm appeared to be maintained while there was a gradual slowing of the sinus rate, for the eventual sinus rate was usually lower than the sinus rate for bigeminal rhythm. This was in obvious contrast to the speeding induced by purely physical manoeuvres, where the sinus rate was almost always higher during sinus rhythm than during bigeminy. In the second case, the transition from bigeminal to sinus rhythm was accomplished solely by speeding the heart.

In both cases, physical exercise and vagal blockade by atropine suppressed the premature ventricular contractions, though it is not clear whether this effect was primarily the result of heart rate *per se* rather than of vagal withdrawal. In Case 2, the voluntary speeding was probably achieved by a combination of vagal and sympathetic changes, which is consistent with earlier reported cases of voluntary tachycardia (Favill and White, 1917; West and Savage, 1918; Ogden and Shock, 1939; Pickering and Gorham 1975). This speeding did not appear to occur merely as a result of changes in muscle tension or respiration, suggesting that some degree of direct voluntary autonomic control was achieved.

To be therapeutically effective, the learned control of any disordered function must be carried over to situations outside the laboratory. The first requisite for this to occur is that the learned behaviour can be performed in the absence of external feedback. Our second case could do this, but the first was unable to do it consistently. The type of control needed for therapeutic benefit may be of two kinds, which are exemplified by our two cases. On the one hand, the disturbance may be relatively continuous and asymptomatic, as was the arrhythmia in Case 1, and as are some other disorders where biofeedback techniques are being applied (e.g. hypertension). In such disorders, the learned control must become relatively continuous, and therefore subconscious. On the other hand, the disturbance may be intermittent and symptomatic, as was the arrhythmia in Case 2. In this type, the

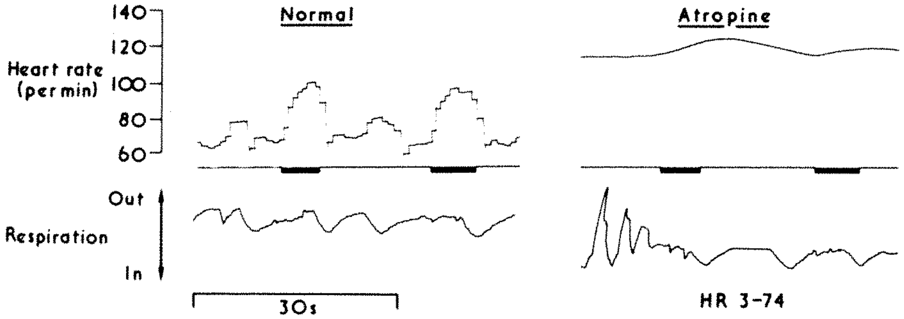

Fig. 6 *Case 2. Five-second attempts at voluntary speeding (signalled by solid bars), before (left) and after (right) atropine.*

learned behaviour need only be performed when the symptoms arise, and a successful suppression of symptoms will tend to reinforce the behaviour pattern. It would be expected that this second type would respond better to biofeedback training than the first, and our two cases would tend to bear this out. It remains to be seen whether such training confers any sustained therapeutic benefit.

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Improvement of symptoms in patients with sick sinus syndrome by spontaneous development of stable atrial fibrillation[1,2]

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Fifty-six patients with symptomatic chronic sinus bradycardia because of sick sinus syndrome (SSS) were followed for periods from one month to 11 years (average 3·2 years). Eleven developed stable atrial fibrillation persisting for 8 to 61 months; 52 had permanent demand pacemakers implanted before atrial fibrillation commenced. In the 11 patients with atrial fibrillation, 10 had adequate ventricular rate, 8 with rates > 100 beats/min requiring digoxin for rate control. The 8 patients with atrial fibrillation with pacemakers remained asymptomatic for 13 to 18 months without requiring reimplantation; battery failure occurred in 2 whose rapid ventricular rates were controlled by digoxin. In the other 6 patients with pacemakers who developed atrial fibrillation, adequate ventricular rates persisted resulting in overdrive suppression. No patient had systemic embolisation. The previous duration of symptomatic sinus bradycardia was longer in patients developing atrial fibrillation (average 5·5 years) compared ($P < 0·01$) with patients without atrial fibrillation (1·9 years). Further, premature atrial contractions occurred in all 11 patients before atrial fibrillation in contrast to only 21 of the 45 patients without atrial fibrillation. It is concluded that occurrence of atrial fibrillation in SSS with symptomatic sinus bradycardia provides a natural cure of symptoms caused by bradycardia. These data indicate that permanent ventricular pacing may not be necessary if persistent atrial fibrillation develops in SSS.

Symptomatic chronic sinus bradycardia in the sick sinus syndrome (SSS) is generally refractory to long-term pharmacological therapy, and in most instances permanent pacemakers are required for the relief of symptoms (Ferrer, 1973). While many aspects of the natural history of this disorder are not well established, it is recognised that sinus node function worsens with time and lifelong pacemaker treatment is, therefore, anticipated. Some patients with SSS are prone to episodes of supra-ventricular tachyarrhythmias including paroxysmal atrial fibrillation; alternating sinus bradycardia and tachycardia, usually supraventricular, is termed the 'bradycardia-tachycardia syndrome' (Short, 1954). The occurrence of transient atrial fibrillation in patients with SSS provides the intriguing possibility that spontaneous or induced stable atrial fibrillation may offer a natural therapeutic mechanism for maintaining an accelerated ventricular response in this entity, thus obviating the need for permanent pacemaker implantation. Indeed, as early as 1954 Short observed that one of his patients with the 'bradycardia-tachycardia syndrome' became asymptomatic upon developing atrial fibrillation and, furthermore, imaginatively suggested that a means for inducing atrial fibrillation in these patients would be of therapeutic value (Short, 1954). Though stable atrial fibrillation has been observed in SSS (Ferrer, 1973; Rubenstein *et al.*, 1972; Krishnaswami and Geraci, 1975), the clinical importance of atrial fibrillation

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in this setting has not been fully realieds. The circumstances, incidence, and consequences relative to the development of persistent atrial fibrillation in SSS are unknown. The present investigation was, therefore, carried out over an 11-year period at our institution in a population of 56 patients with SSS in whom stable atrial fibrillation developed in 11 patients. In this study the clinical features of SSS patients with and without the development of atrial fibrillation are compared.

Methods and results

Fifty-six patients (35 men and 21 women) with electrocardiographic evidence of chronic symptomatic inappropriately slow sinus rates which were either periodic or persistent form the basis of this study. Their ages ranged from 54 to 90 years (average 61 years). The duration of follow-up was from 1 month to 11 years. The severity of the symptoms caused by slow heart rate in 53 patients necessitated insertion of permanent demand ventricular pacemakers whereas in 3 they did not. In all of the 56 patients sinus bradycardia resulted in a variety of symptoms ranging from lethargy and tiredness to frank syncopal episodes. The slow sinus rates were not related to drug therapy including digitalis, propranolol, or reserpine. In addition their heart rates showed inadequate increases after administration of intravenous atropine (Ferrer, 1973). Of the 53 patients, 31 also underwent rapid atrial stimulation for the evaluation of sinus node recovery time (Mandel *et al.*, 1971).

Fig. 1, of patient H.W. with syncopal episodes, exemplifies a severe form of sinus bradycardia in whom the heart rate was only 20 bpm during syncope. The lack of a consistent escape mechanism from the atria, AV junction, or lower pacemaker sites contributes to the genesis of cardiac asystole. This is a frequent finding in SSS and appears to indicate associated disease of sub-sinoatrial nodal structures with depressed automaticity. Fig. 2 shows an example of a very abnormal prolongation of sinus node recovery time in patient R.H. with symptomatic sinus bradycardia. The top panel showed slow sinus rhythm at a rate of 56 bpm. In the bottom tracing the right atrium was paced at 98 bpm; after abrupt cessation of atrial pacing, the sinus node required the extraordinarily long recovery period of 3·26 s to generate a sinus beat.

During the course of follow-up of the 53 patients with persistent SSS, 8 developed atrial fibrillation which has remained stable for 8 to 38 months. Three additional patients presented with chronic atrial fibrillation who, after undergoing electrical cardioversion, emerged with extremely slow sinus or junctional rhythm. In each of these 3 subjects, there was historical and previous electrocardiographic evidence of pronounced symptomatic sinus bradycardia, thereby affording the diagnosis of SSS in retrospect. All 3 patients spontaneously reverted to atrial fibrillation. The pertinent clinical in-

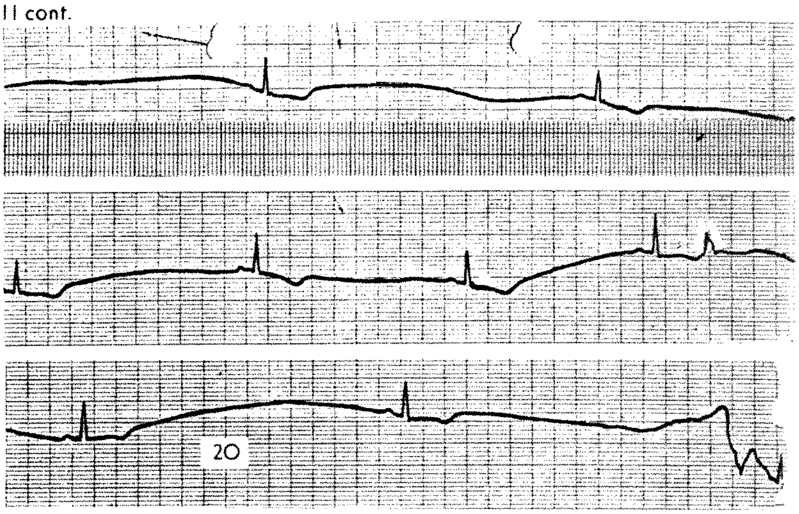

Fig. 1 *Electrocardiogram (lead II) recorded during a period of syncope in patient H.W. with the sick sinus syndrome. The three continuous strips show severe sinus bradyarrhythmia of 20 beats/min with a premature ectopic ventricular beat. The lack of an escape mechanism between the infrequent sinus beats is noteworthy.*

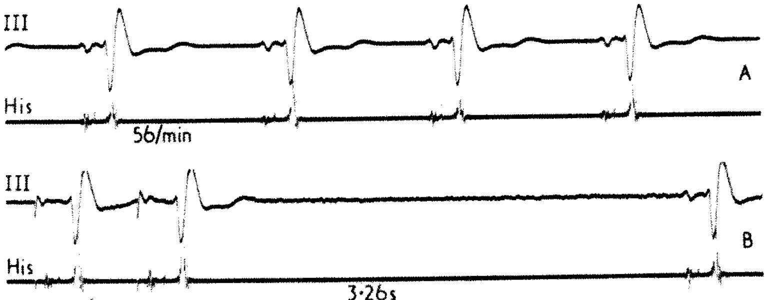

Fig. 2 *Representative tracing of Lead III and the His bundle electrogram showing the sinus node recovery time in SSS patient R.H. The top panel (A) shows sinus bradycardia (rate 56/min). In the bottom panel (B) right atrial pacing was carried out at a rate of 98/min. Abrupt cessation of pacing was followed by a very long pause of 3·26 s during which no escape activity was manifested.*

formation in the 11 patients with SSS and stable atrial fibrillation is presented in Table 1. Selected patients below delineate the characteristic features and modes of presentation in SSS with persistent atrial fibrillation.

(1) SICK SINUS SYNDROME PRESENTING WITH CHRONIC ATRIAL FIBRILLATION

A 67-year-old woman (Case 1, Table 1) presented with atrial fibrillation and a moderately rapid resting ventricular response of 90 bpm (Fig. 3). Her only symptoms consisted of occasional palpitation. Elective cardioversion was carried out; the immediate postcardioversion period showed very slow sinus rate with erratic atrial activity and periods of junctional escape rhythm as shown by the continuous recordings A through E in Fig. 3. The slowest ventricular response was 34 bpm in strips A and B. Her bradycardia responded poorly (< 70 bpm) to 1·5 mg intravenous atropine. During intensive care unit monitoring atrial fibrillation returned within a few hours, and this arrhythmia has remained stable with adequate ventricular response to date. Review of previous electrocardiograms taken elsewhere pointed to atrial fibrillation of at least three months' duration and pronounced sinus bradycardia with periods of sinus arrest for 3 years before onset of atrial fibrillation. In addition, before atrial fibrillation, she had had dizzy spells

Table 1 *SSS with stable atrial fibrillation*

Case No.	*Age (y)*	*Sex*	*SSS duration before AF (y)*	*Duration of AF (mth)*	*Ventricular response during AF*	*APB before AF*	*Associated cardiac disease*
1	67	F	5	61	90	+	None
2	69	M	5	24	160	+	CAD
3	77	M	5	20	105	+	None
4	70	M	11	18	120	+	None
5	67	F	4	8	110	+	AS
6	82	M	6	8	100	+	CAD
7	66	F	3	25	140	+	CAD, HCVD
8	83	F	8	38	30	+	HCVD
9	80	M	5	13	90	+	CAD
10	65	M	3	10	100	+	COPD
11	61	M	5	12	100	+	None

Abbreviations: AF, stable atrial fibrillation; APB, atrial premature beats; +, presence of APB before AF; CAD, coronary arterial disease; AS, congenital aortic stenosis; HCVD, essential hypertension; COPD, chronic lung disease.

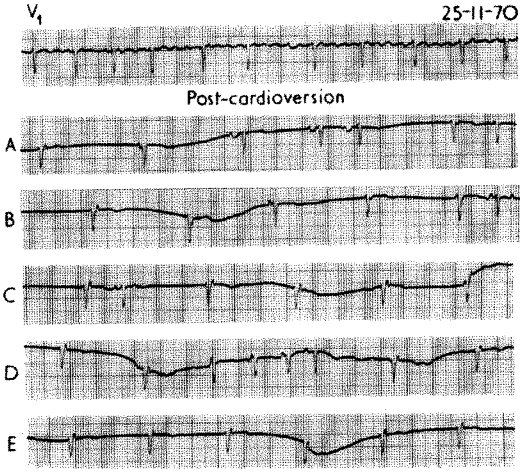

Fig. 3 *Representative lead V1 recording of the emergence of premature atrial beats and escape junctional rhythm (continuous panels A through E) in Case 1 after elective cardioversion of chronic atrial fibrillation (shown in the top panel).*

and periodic weakness for 2 years suggesting SSS for this prolonged period.

Two further patients (Cases 2 and 3, Table 1) presented similarly with atrial fibrillation and after cardioversion had slow sinus rates. In both of these patients, reversion to chronic atrial fibrillation occurred which has persisted to the present time.

(2) SSS WITH PERMANENT PACEMAKERS DEVELOPING STABLE ATRIAL FIBRILLATION AND ADEQUATE VENTRICULAR RESPONSE

Eight of the remaining patients with SSS who developed chronic atrial fibrillation had had permanent pacemakers implanted. In two of these patients (Cases 4 and 9, Table 1) battery failure occurred. However, in view of the stable atrial fibrillation with an adequate heart rate, shown by serial electrocardiograms and two 24-hour periods of ambulatory electrocardiographic monitoring, and the lack of symptoms, pacemaker replacement was not recommended in either patient. Subsequently, both patients remained asymptomatic with an adequate ventricular response in the presence of persistent atrial fibrillation.

Case 4, a 70-year-old man, had had syncope caused by SSS for 4 years before pacemaker insertion. In Fig. 4, the top tracing showed his sinus bradycardia with premature atrial beats in 1969; a permanent pacemaker was installed at that time. By 1974, strips B and C indicated atrial fibrillation with a moderately fast heart rate. Carotid sinus massage, carried out beginning on the right side of strip B and continued into strip C, resulted in slowing of the ventricular response thereby allowing the demand pacemaker to initiate electrical impulses producing ventricular capture (strip C). Seventeen months later, the patient's pacemaker failed; strip D also obtained during carotid massage shows lack of ventricular capture by electrical stimulation (arrows) with atrial fibrillation which has remained stable for 18 months.

Case 9, age 80, showed sinus bradycardia with premature atrial beats in panel A of Fig. 5. A permanent demand pacemaker was inserted because of symptoms of SSS. Subsequently, a normally functioning pacemaker was temporarily inhibited by chest wall stimulation (Barold *et al.*, 1970) thereby revealing underlying SSS (strips B and C). Five months later (strip D) the patient presented with atrial fibrillation and rapid ventricular response which suppressed the demand pacemaker. Though pacemaker failure occurred 6 months later, reinsertion was not recommended since the patient remained in stable atrial fibrillation without symptoms, which continues to be the case.

(3) SSS WITH PERMANENT PACEMAKERS DEVELOPING ATRIAL FIBRILLATION AND INADEQUATE HEART RATE

In only 1 of the 11 patients with SSS who developed stable atrial fibrillation was the ventricular response inadequate. This was an 83-year-old woman (Case 8, Table 1) who presented at our institution in 1972 with atrial fibrillation and a very slow heart rate of

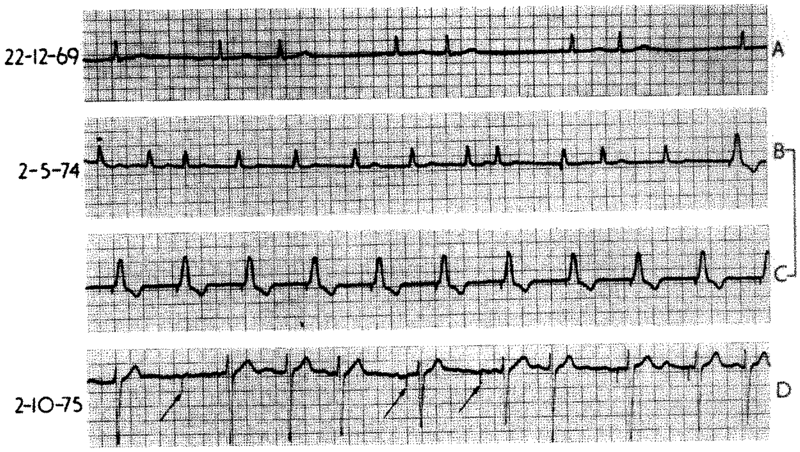

Fig. 4 *Serial tracings in Case 4 with sick sinus syndrome who developed stable atrial fibrillation. Strip A shows sinus bradycardia with frequent atrial beats. Strips B and C are continuous. Stable atrial fibrillation with normal demand pacemaker sensing is documented in strip B. In strip C normal pacing function is unmasked by carotid sinus massage. In strip D atrial fibrillation continues with a moderately slow ventricular response resulting from digitalis therapy and carotid massage; the pacemaker spikes (arrows) fail to capture the ventricle.*

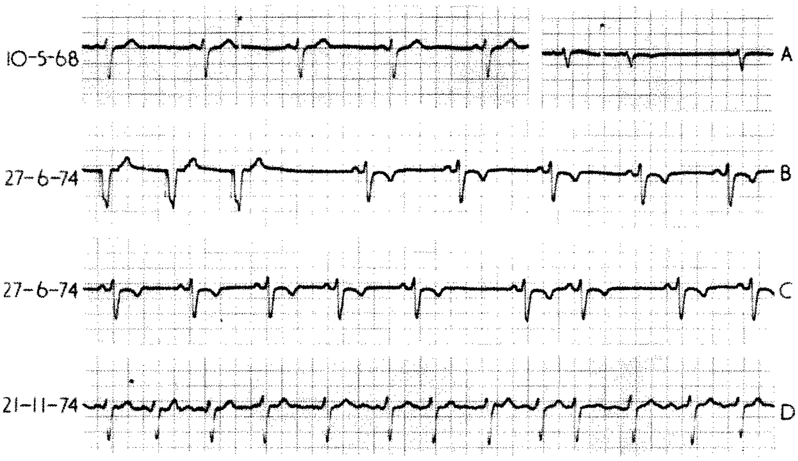

Fig. 5 *Serial rhythm strips in Case 9 with SSS who developed stable atrial fibrillation. SSS was observed on the top panel (A); subsequently a demand ventricular pacemaker was implanted. In the second panel (B) ventricular pacing was temporarily inhibited after the first three beats by the method of chest wall stimulation which resulted in the emergence of SSS (strips B and C). In the bottom panel (D), a representative tracing showed stable atrial fibrillation with a moderately rapid ventricular response.*

20 to 40 bpm (Fig. 6). Because of repeated dizzy spells a permanent pacemaker was inserted. She had an 8-year history of lethargy and syncope. Previous electrocardiograms obtained from another hospital showed the onset of sinus bradycardia in 1963 and long periods of sinus arrest in 1968 (Fig. 6).

Discussion

The present study suggests that the development of stable atrial fibrillation in patients with the sick sinus syndrome (SSS) provides a spontaneous mechanism for the natural cure of the slow heart rate which occurs in this condition. For atrial

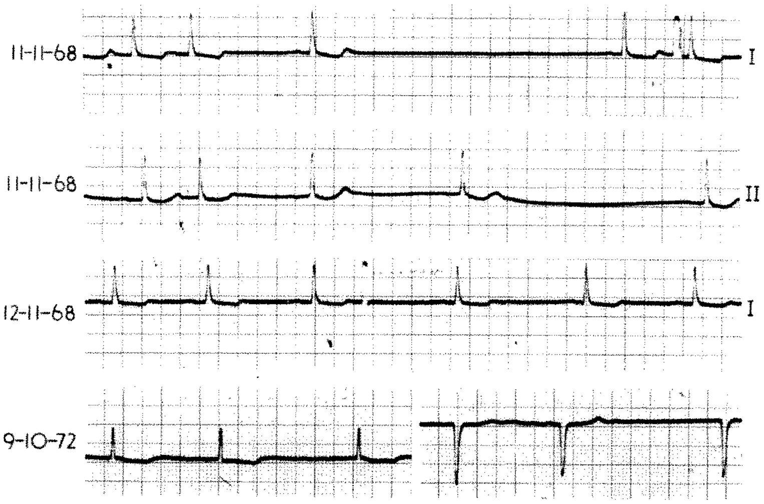

Fig. 6 *Serial rhythm strips in Case 8 with sick sinus syndrome who developed chronic atrial fibrillation. The top three panels indicated periods of sinus arrest and premature atrial beats during which the patient experienced dizziness. The bottom panel shows stable atrial fibrillation but with a very slow ventricular rate of 20 to 40 bpm; her symptoms continued and a permanent demand ventricular pacemaker was inserted.*

fibrillation to afford a beneficial effect, this arrhythmia must be stable with an adequate ventricular response and should not compromise cardiac function or give rise to systemic embolisation. It is important to emphasise that there is an unsubstantiated clinical impression that atrial fibrillation occurring in SSS usually is associated with a very slow heart rate and so that this would be a continuing requirement for a permanent pacemaker. In this regard, our investigation provides evidence to the contrary since 10 of the 11 patients herein who developed stable atrial fibrillation manifested a perfectly adequate ventricular response (Table 1). Only one of our patients required a pacemaker for maintenance of a sufficient heart rate, whereas the remaining 10 continue to date to have clinically adequate ventricular responses. Indeed, 5 SSS patients with stable atrial fibrillation, 3 who had never undergone pacemaker insertion, and 2 with pacemaker failure, now have normal heart rates and remain entirely free of their symptoms which occurred regularly before the onset of atrial fibrillation.

The possibility that atrial fibrillation may appear in patients with sick sinus syndrome has been noted in reviews of this condition (Ferrer, 1973; Krishnaswami and Geraci, 1975). However, the occurrence of this arrhythmia was regarded only as an incidental observation; no special significance was attached to the development of atrial fibrillation in SSS, and information concerning the harbingers and clinical course of this rhythm alteration is lacking.

Our documentation of the development of stable atrial fibrillation in a substantial proportion of patients with SSS, which renders unnecessary the implantation of permanent pacemakers in nearly all of the patients in whom this occurs, raises certain important considerations: (1) elucidation of the factors predisposing to the development of atrial fibrillation in these patients; (2) clarification of the factors responsible for the persistence of atrial fibrillation; (3) identification of SSS patients likely to develop stable atrial fibrillation; (4) prediction of the onset of the arrhythmia in SSS; (5) delineation of the clinical course of atrial fibrillation seen in these patients; (6) determination of the haemodynamic consequences of atrial fibrillation in SSS; and (7) examination of whether systemic embolisation constitutes a hazard with atrial fibrillation in this condition.

To provide the necessary information concerning these considerations, both retrospective and prospective assessment of the features of these patients was carried out. From this analysis, it was possible to determine a group of factors (Table 2) which appeared to be closely related to both the induction and persistence of atrial fibrillation in patients with the sick sinus syndrome. Of the potential factors examined, the duration of SSS symptomatology, the presence of intra-atrial conduction disorders, and previous atrial ectopy were each found to predispose to the subsequent development of chronic atrial fibrillation in SSS. Though the overall prevalence of radiographic or echographic atrial enlargement was infrequent in our SSS patients, 2 of the 4 patients with the finding developed stable atrial fibrillation. Features found to be unrelated to the occurrence of persistent atrial fibrillation in our population included patient age; associated heart disease such as coronary, hypertensive, or rheumatic cardiac involvement; and non-cardiac disorders such as chronic pulmonary disease and hyperthyroidism. In addition, neither the severity of sinus bradycardia nor the presence of a permanent pacemaker correlated with this condition.

Table 2 *Potential factors responsible for onset and persistence of stable atrial fibrillation in SSS*

(1) Age of patient
(2) Type of associated heart disease
(3) Associated non-cardiac disease
(4) Severity of sinus bradycardia
*(5) Duration of symptomatic SSS
(6) Role of permanent pacemaker
*(7) Atrial enlargement
*(8) Intra-atrial conduction abnormalities
*(9) Previous atrial ectopy

*Denotes factors predisposing to stable atrial fibrillation in SSS.

In regard to the correlation of the duration of symptoms of SSS with the onset and perpetuation of atrial fibrillation, the patients developing stable atrial fibrillation had had symptomatic sinus bradycardia for 3 to 11 years (mean of 5·5 years) beforehand (Table 1). In contrast ($P < 0{\cdot}01$), the SSS patients not developing atrial fibrillation had symptoms resulting from sinus bradycardia for only 0·8 to 3·5 years (mean of 2·1 years).

Intra-atrial conduction defects were present in 10 of the 11 patients developing atrial fibrillation (Table 1) compared ($P < 0{\cdot}01$) with only 13 of the 45 SSS patients who remained in sinus rhythm. Disturbances of intra-atrial conduction were diagnosed by the presence of notched widened ($>2{\cdot}5$ mm) P complexes on limb leads I and/or II in the absence of radiographic or echographic left atrial enlargement.

Ectopic premature atrial beats were observed electrocardiographically in all 11 SSS patients before their subsequent development of stable atrial fibrillation (Table 1). Conversely ($P < 0{\cdot}01$) ectopic premature atrial activity was noted in only

21 of the 45 patients with SSS without chronic atrial fibrillation. These data indicate that ecoptic premature atrial systoles are consistent precursors of chronic atrial fibrillation in patients with sick sinus syndrome. The precipitation of atrial fibrillation by premature atrial beats is exemplified by a 46-year-old man who had SSS and episodic atrial flutter-fibrillation (Fig. 7). Brief periods of atrial fibrillation were regularly initiated by premature atrial contractions. Though persistent atrial activity is known to be associated with sinus bradycardia (Goel and Han, 1970), the mechanism of these atrial extrasystoles in SSS is largely speculative. However, their pathogenesis is consonant with the concept of atrial disease in patients with sick sinus syndrome (Ferrer, 1968). In agreement with this is the necropsy finding in SSS of diffuse fibrotic areas in the atria (Rubenstein *et al.*, 1972) which may help to provoke ectopic atrial activity. In addition, this panatrial fibrosis may be responsible for the maintenance of atrial fibrillation. Furthermore, it is rational to assume that the tendency to develop atrial fibrillation increases with the gradual progression of atrial scarring in SSS. These observations are consistent with our findings in the present study that patients with long-standing symptomatic sinus bradycardia are particularly prone to the development of stable atrial fibrillation.

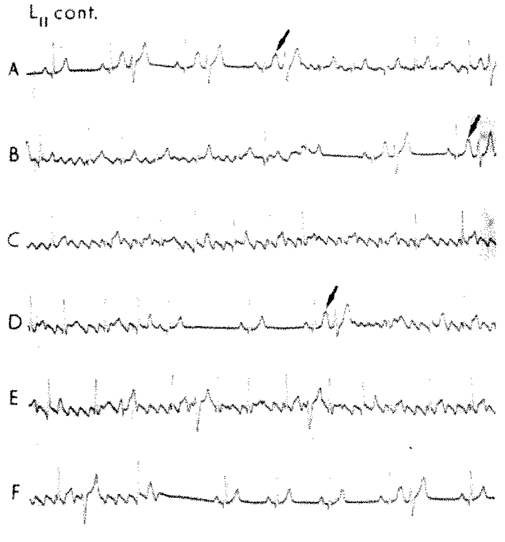

Fig. 7 *Continuous recordings of limb lead II in patient having the sick sinus syndrome with paroxysmal atrial fibrillation. It is noteworthy that all episodes of atrial fibrillation were precipitated by premature atrial beats as seen in strips A, B, and D (arrows).*

The role of sinoatrial node re-entry in the genesis and maintenance of experimental supraventricular tachycardia has been established (Massumi *et al.*, 1973). In view of the finding of delayed sinus node conduction time in SSS (Strauss *et al.*, 1973), the possibility that a sinoatrial re-entry mechanism plays a part in the genesis of premature ectopic extrasystoles and atrial fibrillation in patients with the sick sinus syndrome requires consideration.

From the data presented here, patients with symptomatic sinus bradycardia for longer than 5 years appear to be likely to develop stable atrial fibrillation. In addition, SSS patients displaying premature atrial beats are especially prone to the onset of atrial fibrillation. The presence of both factors, long-standing SSS and premature atrial contractions, probably enhances the prediction of impending chronic atrial fibrillation. The clinical extension of the ability to anticipate generally the onset of stable atrial fibrillation in patients with SSS would be to withhold the insertion of permanent atrial pacemakers; demand ventricular pacemakers should be used instead. Since the development of atrial fibrillation in these patients would render inoperative both the sensing and pacing mechanism of atrial pacemakers, demand ventricular pacemakers would then be required for those with a slow ventricular response.

It is appropriate to emphasise that atrial fibrillation in SSS is often episodic. In this regard atrial fibrillation induced by atrial stimulation in an attempt to establish permanent atrial fibrillation in 3 SSS patients in sinus rhythm was unsuccessful because of reversion to slow sinus rate within 6 hours in each of these individuals. Therefore, atrial fibrillation should be considered stable only after serial 24-hour ambulatory electrocardiographic monitoring has established the persistence of this rhythm for at least 6 months. One of our 45 SSS patients without stable atrial fibrillation who had paroxysmal atrial fibrillation remained in atrial fibrillation for 3 months and then reverted spontaneously to a very slow sinus rate with associated syncope. Similarly, another SSS patient, a 57-year-old man, presented with syncopal episodes. His electrocardiogram showed alternating periods of atrial fibrillation and sinus bradycardia. Spontaneous termination of atrial fibrillation was occasionally associated with prolonged sinus arrest and cardiac asystole (Fig. 8).

While systemic embolisation is a potential complication of atrial fibrillation, none of our patients with SSS and chronic atrial fibrillation has had such an episode. Furthermore, in one large reported series of SSS patients, 4 of 50 patients who had systemic emboli were in sinus rhythm (Rubenstein

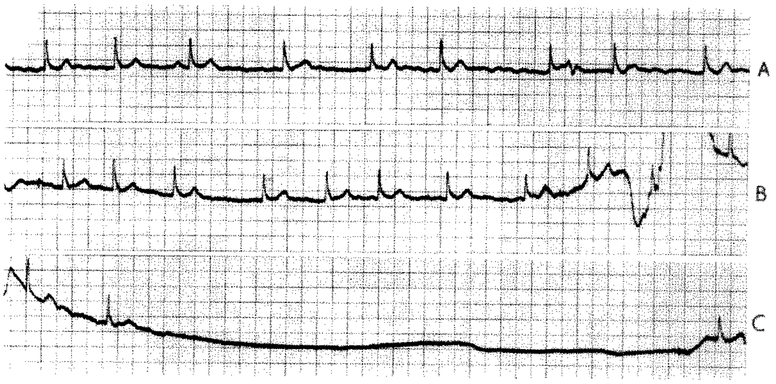

Fig. 8 *Continuous lead II rhythm strips in a patient with SSS and episodic atrial fibrillation. Spontaneous termination of atrial fibrillation in strip C was followed by a long pause of cardiac asystole lasting 8 seconds. Remarkably, no escape focus emerged during this prolonged period of sinus arrest.*

et al., 1972). To date, systemic embolisation has not been encountered in any patient with SSS and stable atrial fibrillation. Therefore, it does not appear that SSS patients with atrial fibrillation have a special tendency for developing arterial emboli, and thus we do not recommend prophylactic anticoagulation in these patients.

It is concluded from the present investigation of a large group of SSS patients that: (1) development of stable atrial fibrillation in patients with SSS is not uncommon; (2) frequent periods of 24-hour ambulatory electrocardiographic monitoring should be undertaken to assess stability of atrial fibrillation; (3) permanent pacemaker therapy should not be discontinued unless persistent atrial fibrillation is present for more than 6 months; (4) in the absence of concomitant AV conduction disturbances, documentation of stable atrial fibrillation in SSS precludes the necessity of continued pacemaker therapy; and (5) the possibility of SSS should be considered in the elective cardioversion of atrial fibrillation so that one is prepared to treat any unmasked serious sinus bradyarrhythmia.

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Circulatory reflexes in myocardial infarction

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The Valsalva manoeuvre was used to examine circulatory reflexes in 22 patients with acute myocardial infarction. Four patients had the 'square wave' response of cardiac failure and two responded normally to the manoeuvre. In the remaining 18 patients there was a 20 per cent or more fall in pulse pressure during the manoeuvre, but no ensuing rise in diastolic pressure, implying impairment of vasoconstriction. This impairment cannot be explained by acidosis, hypocapnia, or arterial hypoxaemia but may be explained by reflex inhibition of vasoconstriction. This abnormal response has important implications when transporting patients; furthermore, it could explain the rapid deterioration sometimes seen in patients with arrhythmias.

Reflexes arising from the heart could impair the normal response of the peripheral circulation to a reduced cardiac output and could explain the frequently observed failure of systemic vasoconstriction to compensate adequately for the fall in cardiac output after myocardial infarction (Smith *et al.*, 1954; Lee, 1957; Thomas *et al.*, 1966; Ramo *et al.*, 1970). This concept was not confirmed by earlier animal experiments (Levy and Frankel, 1953; Wegria *et al.*, 1954), but more recent ones have shown that reflexes arising in infarcted myocardium inhibit reflex vasoconstriction (Costantin, 1963; Kolatat *et al.*, 1967; Toubes and Brody, 1970). It is an attractive hypothesis to suggest that similar impairment of vasoconstriction occurs in man, but the general anaesthesia, the difference in autonomic responses in animals, and the technique of inducing myocardial infarction in these animal experiments are such that these observations may not be entirely applicable to man. However, there is clinical evidence to support the idea of an autonomic disturbance after myocardial infarction in man (Webb *et al.*, 1972). The present study has attempted to seek evidence of impairment of circulatory reflexes in man after myocardial infarction. The Valsalva manoeuvre was used for this purpose as it could be easily applied at the bedside and has been used successfully without harm to the patient to detect heart failure in angina (Elisberg, 1963) and in myocardial infarction (Lee, 1957).

In normal subjects when the intrathoracic pressure is raised during the Valsalva manoeuvre there is a prompt fall in pulse pressure, and as a consequence of stimulation of the baroreceptor reflex there is vasoconstriction and an increase in pulse rate. Persistence of vasoconstriction for a few moments after the return of intrathoracic pressure to normal at the finish of the manoeuvre coupled with an increase in venous return results in an increase in diastolic pressure above control levels—the so-called 'overshoot' phase. Two types of abnormal response have been recognised: (1) the 'square wave' response of cardiac failure in which there is no fall in pulse pressure and no ensuing rise in diastolic pressure during the overshoot phase, and (2) an abnormal response where, despite a fall in pulse pressure during the manoeuvre, there is no reflex vasoconstriction, and as a consequence no increase in diastolic pressure during the overshoot phase. The impairment of the baroreceptor reflex in this latter situation also results in either no, or only a small, increase in heart rate during the manoeuvre.

Patients and methods

Acute myocardial infarction was diagnosed in 22 men aged between 42 and 69 years (mean = 57 years) on the basis of a characteristic history, unequivocal electrocardiographic evidence, and a subsequent diagnostic rise in either serum creatine phosphokinase or hydroxybutyric dehydrogenase. Patients with chronic respiratory disease, previous cardiac failure, or those who had received morphine in the previous four hours, were excluded as these factors may influence the response to the Valsalva manoeuvre. The nature and purpose of the study was carefully explained to each patient and their consent

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obtained. An 18 gauge 5 cm 'teflon' catheter ('Longdwel' Becton, Dickinson Inc.) was inserted percutaneously under local anaesthesia into a brachial artery and connected to a pressure transducer connected to a preamplifier and a direct writing recorder (Devices Instrument Ltd.). The zero level was adjusted to 10 cm below the sternal angle with the patient resting comfortably with the shoulders raised to a semi-recumbent position. Patients were shown how to carry out the manoeuvre, and after several trial attempts, with intervening rest periods, the intra-arterial pressure was recorded continuously before, during, and after the manoeuvre. The Valsalva manoeuvre was performed by supporting a 40-mm column of mercury for as long as possible and in all cases for at least 10 seconds. The following measurements were made from the recording: (1) systolic and diastolic pressures and heart rate in the control period, (2) the minimum pulse pressure during the manoeuvre, (3) the maximum diastolic pressure immediately after the manoeuvre, and (4) the maximum increase in heart rate during the manoeuvre. From the measurements the following were calculated: (1) percentage decrease in pulse pressure during the manoeuvre, (2) percentage increase in diastolic pressure after the manoeuvre, (3) the percentage increase in heart rate during the manoeuvre, (4) the ratio of the percentage increase in heart rate to the percentage decrease in pulse pressure, and (5) the ratio of the percentage increase in diastolic pressure after the manoeuvre to the percentage decrease in pulse pressure.

Arterial blood was analysed in 20 patients for *p*H, carbon dioxide, and oxygen tension using a Radiometer blood gas and *p*H analyser (Model 27).

Results

Individual and mean results are shown in the Table. Four patients (Cases 3, 10, 11, 13) had a less than 20 per cent reduction in pulse pressure and the configuration of their response corresponded to the 'square wave' response of cardiac failure (Sharpey-Schafer, 1955). The remaining 18 showed their ability to perform the manoeuvre by a prompt reduction of at least 20 per cent in pulse pressure and 16 of them achieved a reduction of over 40 per cent. Despite this substantial fall in pulse pressure during the manoeuvre, only 2 had a normal rise in diastolic pressure during the overshoot phase when compared with the data compiled in 360 normal subjects by Sharpey-Schafer and Taylor (1960). Fifteen patients had a less than 15 per cent rise in diastolic pressure during the overshoot phase and in 7 patients there was a change of only 2 mmHg or less (Fig. 1). The majority (89%) had evidence of an impaired rise in diastolic pressure during the

Table *Results of Valsalva manoeuvre in individual patients*

Case No.	*Age (y)*	*Systolic BP*	*Diastolic BP*	*Control pulse pressure*	*Valsalva pulse pressure*	*Per cent reduction in pulse pressure*	*Diastolic pressure after Valsalva*	*Per cent increase in diastolic pressure*	*Control HR*	*Per cent increase in HR*	*[H+] (nmol/l)*	P_{CO_2}	P_{O_2}
1	61	97	48	49	21	57	58	21	106	0	32	33	60
2	59	136	82	54	18	67	92	12	94	33	36	31	63
3	40	84	60	24	20	17	56	−7	76	20	—	—	—
4	64	154	85	69	37	46	86	1	72	0	35	27	80
5	66	162	87	75	58	23	100	15	104	0	37	38	56
6	45	129	94	35	17	51	98	4	63	11	31	23	90
7	42	124	72	52	22	58	89	17	60	20	41	34	76
8	69	122	76	46	11	76	80	5	72	10	33	32	63
9	49	100	55	45	16	64	100	82	112	0	40	34	66
10	65	113	68	45	40	11	67	−1	78	0	39	29	70
11	54	175	97	78	75	4	100	3	60	12	39	35	79
12	53	140	81	59	10	83	87	7	69	20	39	34	71
13	57	181	100	81	66	18	109	9	64	9	—	—	—
14	59	145	85	60	18	70	97	14	116	30	39	33	72
15	62	98	57	41	24	41	55	−4	52	15	35	31	62
16	62	125	85	40	14	65	100	18	80	25	39	34	80
17	58	102	55	47	15	68	64	16	69	30	50	42	71
18	57	75	48	27	12	55	48	0	100	0	45	40	71
19	55	165	80	85	19	78	102	28	72	27	45	37	88
20	63	81	50	31	18	42	49	−2	88	20	37	33	55
21	60	115	65	50	39	22	66	1	68	0	42	37	53
22	57	146	92	54	25	54	92	0	108	17	40	30	88
Mean	57·1	125 9	73 7	52 1	27 0	48·7	81 6	11 9	81 0	13 6	38·7	33 3	70 7
SEM	1 62	6·52	3·56	3 65	3·88	4·99	4·22	3·75	4·09	2 43	0·98	0 94	2 37

Pressure measurements are given in mmHg.

overshoot phase. There was no correlation between the magnitude of the diastolic overshoot and (a) the site of myocardial infarction, (b) the arterial pressure, (c) hydrogen ion concentration, (d) arterial carbon dioxide tension, or (e) arterial oxygen tension.

In addition to reflex vasoconstriction, the Valsalva manoeuvre results in an increase in heart rate in normal subjects during the manoeuvre. Five of the 18 patients in whom pulse pressure fell during the manoeuvre had a 20 per cent or more increase in heart rate and could be regarded as having a normal response, but in the remaining 13 (72%) the response was impaired (Fig. 2). In general those with the smallest rise in diastolic pressure in the overshoot phase were the same patients as had the least rise in heart rate during the manoeuvre but there was a pronounced disparity in 4 patients (Cases 3, 12, 20, and 22). These 4 patients had a rise of less than 10 per cent in diastolic pressure yet heart rate increased by up to 20 per cent during the manoeuvre.

Arterial carbon dioxide tension was below 35 mmHg in 14 (70%) but hydrogen ion concentration was within the normal range. Ten patients had an arterial oxygen tension below 70 mmHg. None of these variables had a statistical correlation with either the percentage rise in diastolic pressure during the overshoot phase or the percentage rise in heart rate during the manoeuvre.

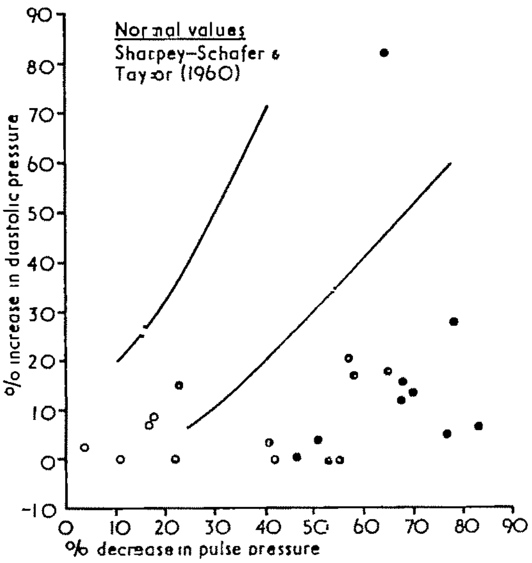

Fig. 1 *Relation between the decrease in pulse pressure during the Valsalva manoeuvre and the increase in pulse pressure in the 'overshoot' phase at the cessation of the manoeuvre. The curved lines represent the upper and lower limits found by Sharpey-Schafer and Taylor (1960) in 360 normal subjects. The open symbols represent 4 patients with a 'square wave' response indicating cardiac failure.*

Discussion

It was not surprising, in view of the frequent occurrence of left ventricular failure after myocardial infarction, to find 4 patients with the 'square wave' response of cardiac failure; a similar response has been observed in the past in some patients with myocardial infarction (Lee, 1957). The remaining 18 patients, by virtue of the 20 per cent or more reduction in pulse pressure during the manoeuvre, showed their ability to carry out the manoeuvre adequately and that their hearts were capable of responding to a reduced filling pressure. The vasoconstriction and concomitant increase in diastolic pressure during the overshoot phase expected from this reduction in pulse pressure did not occur in 16 patients (89%) implying impairment of the baroreceptor reflex; the remaining 2 had a normal vasoconstrictor response. Further evidence of impaired circulatory reflexes was derived from the failure of the heart rate to increase in response to the fall in pulse pressure during the manoeuvre. The disparity, in three cases, between heart rate response and diastolic pressure response

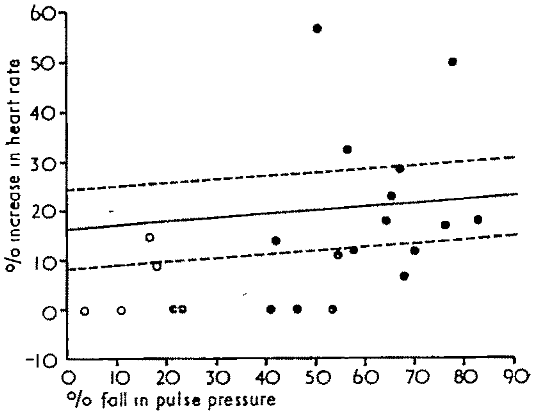

Fig. 2 *The relation between decrease in pulse pressure and the increase in heart rate during the Valsalva manoeuvre. The regression line for subjects of a comparable age has been calculated from the data of Gross (1970) and the 95 per cent prediction limits are shown by the broken lines. The open symbols represents the 4 patients with a 'square wave' response, as in Fig. 1.*

has been noted in other clinical conditions but its explanation is unclear (Gross, 1970).

There are a number of possible explanations for the impaired circulatory response to the manoeuvre: (1) the effect of age, (2) impairment of nerve transmission, or response, to sympathetic stimulation, or (3) central inhibition of the baroreceptor reflex. The baroreceptor reflex is impaired with ageing (Gross, 1970; Gribbin *et al.*, 1971), but this effect does not appear sufficient to account for these observations in patients with myocardial infarction. It is possible that the baroreceptors themselves could be abnormal after myocardial infarction, and by failing to respond to the reduced pulse pressure result in an impaired vasoconstrictor and heart rate response. Sympathetic nerve transmission and the reactivity of blood vessels is affected by severe metabolic acidosis, hypocapnia, or hypoxia, but as these variables were only marginally abnormal it is doubtful if the reflex was impaired in this way. Very high levels of catecholamines produced by infusion into animals can produce maximum vasoconstriction and thereby prevent any further vasoconstriction in response to the Valsalva manoeuvre (Sarnoff *et al.*, 1948) but the levels of circulating catecholamines after myocardial infarction are unlikely to approach the levels attained during those animal experiments. Significant levels of circulating vasodilators have not been shown in myocardial infarction in man and are an equally unlikely explanation.

The baroreceptor reflex can be suppressed in animals by stimulation of the hypothalamic areas concerned with the 'defence reaction' (Hilton, 1963; Gebber and Snyder, 1970); it is not known whether severe illness in man provokes similar suppression. Reflex inhibition of vasoconstriction has been shown in experimental coronary occlusion in animals (Costantin, 1963; Toubes and Brody, 1970). The inhibitory stimuli are thought to arise in the myocardium or coronary vessels. Myocardial receptors can be shown in animals by histological techniques (Hirsch and Borghard-Erdle, 1961) and by recording impulse activity in the afferent nerves of the heart (Paintal, 1963; Sleight and Widdicombe, 1965; Malliani *et al.*, 1972; Öberg and Thoren, 1972). Similarly, receptors have been shown in coronary vessels (Brown, 1967). Whether similar receptors and reflexes exist in man is unknown but if they do so a similar reflex inhibition could account for the present finding.

The impairment of circulatory reflexes after myocardial infarction may be a factor in causing hypotension, and when cardiac output is reduced by arrhythmias it may explain the rapid deterioration of these patients. Furthermore, it is important to avoid rapid changes in posture during transportation as these patients will be unable to adjust the circulation as quickly as normal subjects. Recent work has been concerned with the parasympathetic nervous system and its role in arrhythmias (Webb *et al.*, 1972), but the findings presented here suggest impairment of the function of the sympathetic nervous system also.

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P loops during common and uncommon atrial flutter in man[1]

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Atrial flutter has never been satisfactorily defined. The 'common' pattern of flutter was originally described by Lewis in 1913. Less frequently observed forms of flutter are termed 'uncommon'. Sixteen cases of the 'common' and 6 of the 'uncommon' type have been studied using isolated P loop vectorcardiography. All patients had some degree of atrioventricular block but none had evidence of digitalis excess. The atrial rates were regular and were in a range between 250 and 330/minute. Vagal manoeuvres increased AV block in each instance. All those with the 'common' type of flutter had P loops with a caudad-cephalad orientation and fifteen of the sixteen had forces which descended over the right atrium and ascended over the left atrium. The 6 cases of the uncommon type of flutter had rates which ranged between 250 and 300/minute and did not fulfil both of the criteria for 'common' flutter; namely continuous baselineu ndulation and prominent negative P deflections in the inferior leads. The cases with the 'uncommon' type of flutter had a variety of loop patterns. The most frequent type was oriented inferior slightly to the right and anterior. One patient satisfied criteria for left atrial flutter. In another the loop was oriented inferior leftward and anterior. The vectorcardiogram provides a rich source of descriptive data but does not identify the underlying mechanism(s) of flutter.

Fluttering of the atrium was visualised in animals by MacWilliam (1887) and subsequently recorded by string galvanometer in man by Jolly and Ritchie (1911). In 1913 Sir Thomas Lewis presented electrocardiographic criteria of atrial flutter which are still valid. He described the most frequent form of flutter which is now termed 'classical', 'common', or 'typical'. Less frequently observed patterns of atrial excitation during flutter have been termed 'uncommon', 'rare', or 'atypical'. One obvious difference between the two forms of flutter is that of P wave (flutter wave) morphology and the influence of the P waves on the baseline. Though there does not appear to be an obvious difference between the common and uncommon varieties of flutter in their response to physical or pharmacological interventions, there may be subgroups which vary in mode of onset, maintenance, and termination.

Sir Thomas Lewis restricted his observations, and thus his definition, to the pattern of the common type of flutter. Most electrical patterns of the 'uncommon' type of flutter do not resemble that of 'common' flutter and consequently do not accord with the historic description of flutter. The dilemma is evident as Marriott and Myerburg, 1974, state in Hurst and Logue's basic cardiac text, 'atrial flutter has never satisfactorily been defined'.

In this study two electrocardiographic criteria were required for the diagnosis of 'common' flutter; namely a continuous undulation of the baseline and a prominent negative component of the P waves in leads II, III, and aVF (Lewis, 1913, 1925; Katz and Pick, 1956). Flutter was considered to be of the 'uncommon' variety if both criteria were not fulfilled.

There are several electrocardiographic description of the 'common' and 'uncommon' patterns of flutter. However, in a search of the published material, the authors were able to find only 19 vectorcardiographic descriptions of atrial excitation during naturally occurring flutter in man, of which 18 were examples of 'common' flutter and only one

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an example of 'uncommon' flutter (Dechard *et al.*, 1945; Rosen *et al.*, 1969; Alderman *et al.*, 1972; MacLean *et al.*, 1973). Actual P loops, as opposed to derived loops, had been recorded in only 13 patients.

It is the purpose of this report to present a comprehensive analysis of the spatial vectorcardiograms of atrial excitation during flutter in 22 patients of whom 16 had the 'common' type of flutter and 6 had the 'uncommon' type.

Patients and methods

All patients had stable atrial flutter and were without evidence of digitalis excess. Atrial rates were regular and had a range of 250 to 330 cycles/minute. Vagal manoeuvres increased atrioventricular block in each instance. Electrocardiographic criteria for 'common' flutter followed the definitions of Lewis (1913, 1925), as refined by Katz and Pick (1956). The fluttering P waves were regular with identical size, spacing, and contour. The baseline was 'sawtoothed' with continuous undulation most noticeable in leads II, III, aVF, and less noticeable in lead I. An obvious negative component to the undulating pattern was present in leads II, III, and aVF.

The electrocardiographic criteria for 'uncommon' flutter followed in part the observations of Prinzmetal *et al.* (1952). An isoelectric interval was frequently noted between the flutter waves. The baseline did not need to be in constant motion nor was there a requrement for a prominent negative deflection in leads II, III, and aVF.

The study group comprised 17 men and 5 women. The average age of all patients was 67 years, with the average of women being 68 years and that of men being 63 years. The types of underlying heart disease were atherosclerotic coronary disease in 16 patients, rheumatic heart disease with mitral valve involvement in 5 patients, and no identifiable cardiac disease in one patient. The average age of the 16 patients in the 'common' flutter subgroup was 62 years. The 6 patients in the 'uncommon' flutter subgroup had an average age of 69 years and consisted of 4 women and 2 men.

Electrocardiograms and P loops were recorded sequentially during atrial flutter. Five patients also had electrocardiographic and vectorcardiographic P loops after conversion to normal sinus rhythm. Standard 12-lead electrocardiograms were recorded at a paper speed of 25 mm/second. Orthogonal leads and P loops were recorded with the Frank system on a Sanborn 1507A vector system and Hewlett-Packard C04-197A oscilloscopic camera. The X, Y, and Z leads were recorded at a sweep speed of 100 mm/second and calibrated for a 1·0 mV/cm deflection. The vector recording system had an adjustable 'gate' which permitted the isolation and display of the P wave. P loops were displayed and recorded at 0·05 mV/cm with dash-time intervals of 2·5 ms. The blunt end of the tear drop represented the advancing edge.

One patient in the series with 'common' atrial flutter was studied before open heart surgery for correction of mitral regurgitation secondary to papillary muscle infarction. Pacing electrodes were placed on the left atrial appendage at the operation for the control of the heart during the postoperative period. On the eighth postoperative day, P loops were obtained during atrial pacing from the electrodes on the left atrial appendage.

Results

The results are summarised in the Table and Fig. 1. According to the criteria given above, sixteen patients had 'common' atrial flutter. In the standard electrocardiogram, these cases had an undulating baseline with a 'sawtoothed' pattern of atrial excitation and an obvious negative undulation in leads II, III, or aVF (Fig. 2A). P loops were oriented superiorly slightly to the right and slightly posteriorly (Fig. 1 and 2B). The average mean axis was –96° in the frontal plane and –83° in the left sagittal plane. Frontal plane loops were predominantly counterclockwise (10/16).

'Uncommon' flutter occurred in 6 patients (Fig. 1). In contrast to 'common' flutter, the P waves were discrete in 5 of the cases with positive deflections in leads II, III, or aVF (Fig. 3, 4A). In these 5 patients the average mean P loop is depicted in Fig. 4B. One of the 'uncommon' flutter patterns satisfied Mirowski and Alkan's (1967) definition for left atrial flutter. The electrocardiogram showed P waves with a dome-dart configuration in lead V1 and a negative P wave in lead aVL. The P loop had the most rightward and anterior orientation of the 'uncommon' flutter patterns (Fig. 5A, 5B). The sixth patient with 'uncommon' flutter was so distinct and unusual to be considered separately. The flutter was the most rapid of all 22 cases (330/minute). The P waves were almost diphasic in the inferior leads as well as in lead I (Fig. 6A). The P loops were closed with the mean axis inferior to the left and anterior. The frontal P wave axis was +22° and the left sagittal axis was +129° (Fig. 6B).

The four patients with 'common' flutter who also had P loop study during normal sinus rhythm were noted to have normal atrial excitation during sinus rhythm.

Table *Characterisation of patients and flutter*

Case No.	*Age (y)*	*Sex*	*Cardiac disease*	*Drugs*	*Atrial rate*	*NSR 'P' loops* *F°*	*SL°*	*Flutter 'P' loops* *F°*	*SL°*	*Counterclockwise SL loop*
Uncommon flutter										
1	74	M	CAD, MI	None	250			+90	+66	+
2	70	M	CAD, MI	Digoxin	300			+79	+105	−
3	67	M	CAD	Digoxin	300			+101	+105	+
4	58	M	CAD	None	280			+77	+86	−
5	67	F	RHD, MVD	Digoxin	250			+131	±180	+
6	77	F	CAD	Digoxin	330			+22	+129	−
Common flutter										
7	72	M	CAD	Digoxin	300	94	71	−94	−76	+
8	65	M	CAD	Quinidine	280	81	93	−104	−101	−
9	55	M	CAD, MI	Digoxin	250	49	131	−103	−80	−
10	65	M	CAD	None	300	106	40	−92	−62	−
11	65	F	RHD, MVD	Digoxin	280			−92	−46	+
12	62	M	RHD, MVD	Digoxin	300			−82	−85	+
13	82	M	CAD	Digoxin	250			−80	−103	+
14	57	M	CAD	Quinidine	300			−112	−81	+
15	49	M	RHD	Digoxin	300			−74	−93	+
16	58	M	RHD, MVD, AVD	Digoxin	250			−96	−58	+
17	32	M	None	None	315			−88	−77	+
18	70	M	CAD	Digoxin	300			−91	−101	+
19	64	M	CAD	Quinidine	300			−110	−58	+
20	78	F	CAD	Digoxin	300			−132	−121	+
21	53	F	CAD	Procainamide	300			−96	−102	+
22	63	M	CAD	None	300			−93	−80	+

NSR, normal sinus rhythm; M, male; F, female; CAD, coronary arterial disease; MI, myocardial infarction; RHD, rheumatic heart disease; MVD, mitral valve disease; AVD, aortic valve disease. F = frontal; SL = left sagittal.

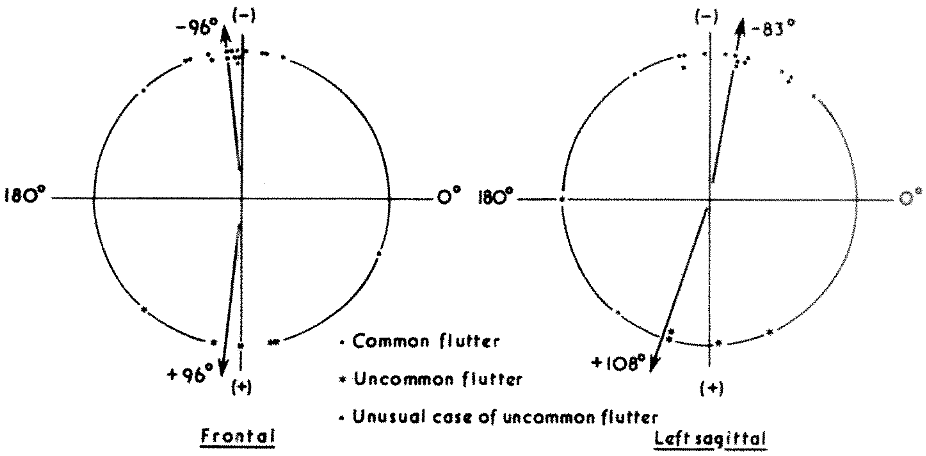

Fig. 1 *Summary figure. Sixteen patients with 'common' flutter P loops had a superior axis in the frontal (−96°) and left sagittal (−83°) planes. Six patients with 'uncommon' flutter had an inferior axis. Five cases of 'uncommon' flutter were similar with frontal plane axis of +96° and left sagittal axis of +180°. One unusual case of 'uncommon' flutter is considered separately.*

Discussion

Human atrial flutter was first described in 1911 by Jolly and Ritchie. Sir Thomas Lewis (1913) later elaborated on the electrocardiographic description. 'The electrocardiograms which represent the auricular activity are peculiar in more respects than one . . . The auricular complexes in leads II and III are always contiguous that is to say, the separate electrical complexes are so close together that the end of one marks the beginning of the next. The string is in constant motion; there are no isoelectric stretches dividing one auricular electrical cycle from the next.

'The auricular complexes in auricular flutter are remarkable for their constancy of form from case to case. . . P in lead I is either a small and pointed summit, or is so insignificant that it cannot be found. P in leads II and III run on either side of the adjacent complexes, so that a series of such complexes forms a continuous wavy or zigzag line. . .'

Citing experimental observations of flutter in animals, Lewis *et al.* (1920) found that the atrial rate was rapid with a high grade of regularity (0·001 to 0·003 second variation). In addition, auricular complexes were contiguous and uniform in outline. They concluded that, 'It seems desirable that the unqualified term "auricular flutter" should be confined to mechanisms of this kind'. Later, Lewis (1925) expanded on the description of the electrocardiogram as follows:

'Leads II and III ascend sharply to a blunt summit and return more gradually. Lead I is diminutive. The complexes are contiguous. The string is moving continuously and rests for no measurable period on a baseline; as soon as one complex is completed, the next one starts'.

Lewis believed that the arrhythmia resulted from continuous excitation waves which travelled in a circuit; a so-called circus movement. Based upon one experiment in man, performed with simultaneous recording of bipolar electrograms in three planes, Lewis *et al.* (1921) concluded that the circus movement travelled down the right atrium and up the left atrium. Using similar techniques, Cabrera and Sodi-Pallares' (1947) findings were similar in 15 of 16 cases of classical flutter. Their report is of special interest because these eminent electrocardiographers concluded that the exceptional case was most likely one of paroxysmal tachycardia. Marriott and Myerburg's (1974) statement regarding the lack of definition of flutter is thereby reinforced because the exceptional case must have fulfilled electrocardiographic criteria for classical flutter to have been entered into the study.

Direct exploratory mapping of hearts with the 'common' flutter pattern has been performed twice at the time of surgery. In one instance there was agreement with surface recordings in showing that excitation advanced down the anterior and lateral right atrium and up the posterior left atrium

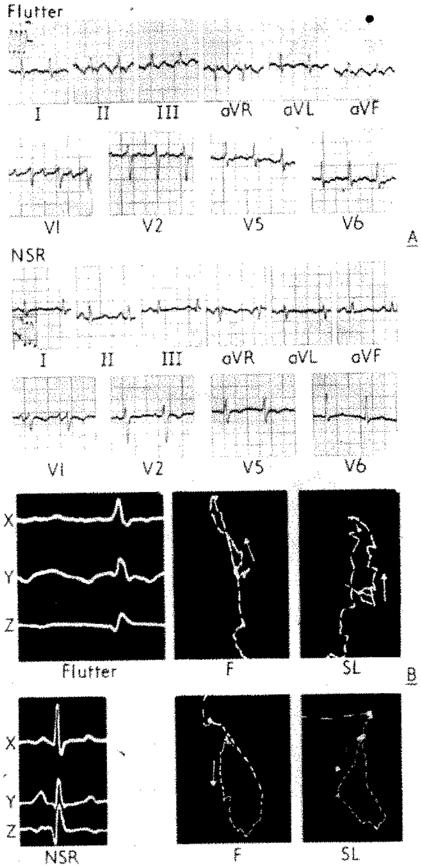

Fig. 2 *(A) Top panel: Electrocardiogram of 'common' atrial flutter. Flutter waves result in an undulating baseline with prominent negative deflections in the inferior leads. Bottom panel: electrocardiogram after reversion to normal sinus rhythm. P waves have a normal orientation and are positive in the inferior leads (Case 9). (B) Vectorcardiogram of 'common' flutter reveals a mean frontal plane axis of −104° and left sagittal plane axis of −101°. The frontal plane loop is in a figure-of-eight. The loop is moving in a caudad to cephalad direction, rightward and slightly anterior. Vectorcardiogram during sinus rhythm reveals a frontal plane axis of +81° and a left sagittal axis of +93°. The loop is moving in a superior to inferior direction from right to left and slightly anterior (Case 8).*

(Rytand, 1966); in the other case, excitation did not proceed in a circuit but rather radiated from low in the atria (Wellens *et al.*, 1971).

Of the 12 reports of classical flutter that we have found with illustrative P loops (Decherd *et al.*, 1945; Rosen *et al.*, 1969; Alderman *et al.*, 1972; MacLean *et al.*, 1973), all have had a loop with an anterior component directed inferiorly and a posterior component directed superiorly. Such was also the case in all but one of our examples of 'common' flutter. The direction of the P loops representing 'common' atrial flutter generally conformed to that described by Lewis. It is of interest that the possibility of reversal of the loop, as noted by Cabrera and Sodi-Pallares (1947) and by our exception, was anticipated by Lewis *et al.* (1920). In contrast to 'common' flutter, MacLean *et al.*'s (1973) sole case of 'uncommon' flutter had a posterior component of the loop which advanced inferiorly and an anterior component which advanced superiorly. Similarly, our series of

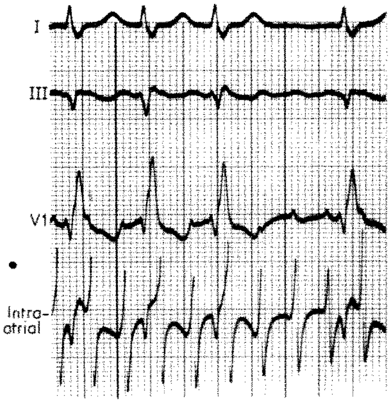

Fig. 3 *Electrocardiogram of 'uncommon' flutter. Simultaneous standard leads I, III, and V1 and intra-atrial lead show atrial excitation at a rate of 300 per minute with positive deflections in lead III separated by isoelectric intervals (Case 3).*

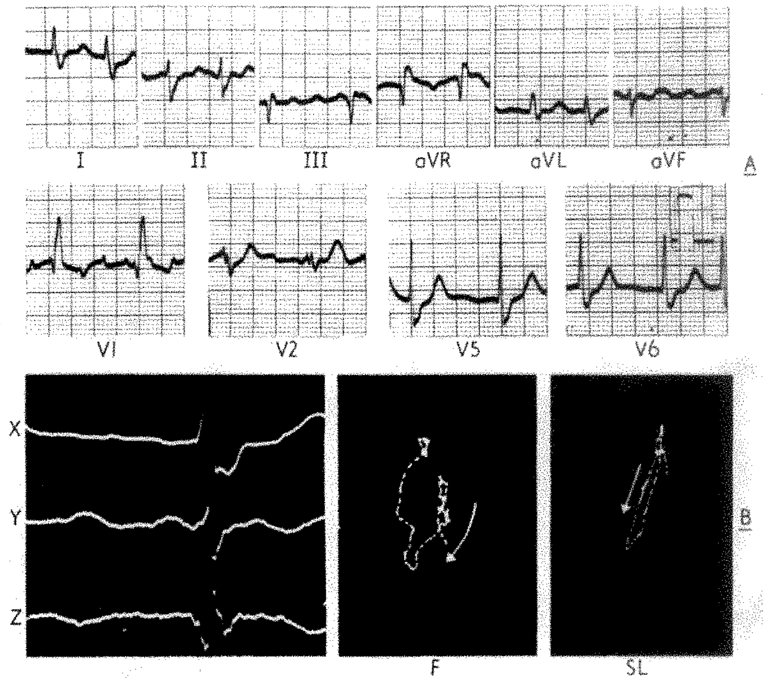

Fig. 4 *(A) Electrocardiogram of 'uncommon' flutter. Positive P waves are present in the inferior leads. Isoelectric intervals are better seen in Fig. 3 (Case 3). (B) P loop of 'uncommon' flutter. Atrial excitation is oriented inferior, slightly to the right and slightly anterior. Frontal plane axis +101°, left sagittal plane +105° (Case 3).*

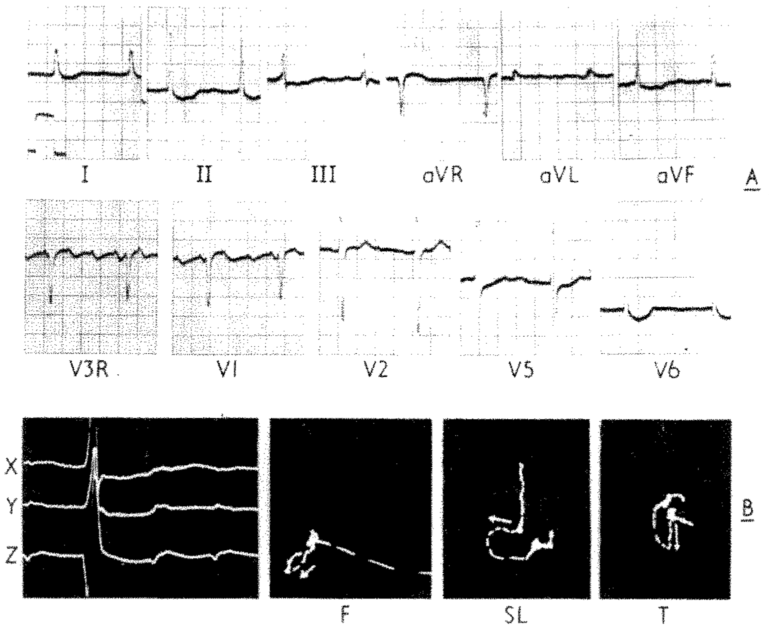

Fig. 5 *(A) Electrocardiogram of 'uncommon' (left atrial) flutter. The P wave is negative in aVL and V6 and has a dome-dart configuration in lead V1 (Case 5). (B) Vectorcardiogram of 'uncommon' (left atrial) flutter. The P loop is orientated inferior, to the right, and anterior. Frontal plane axis +131°, left sagittal plane axis +180° (Case 5).*

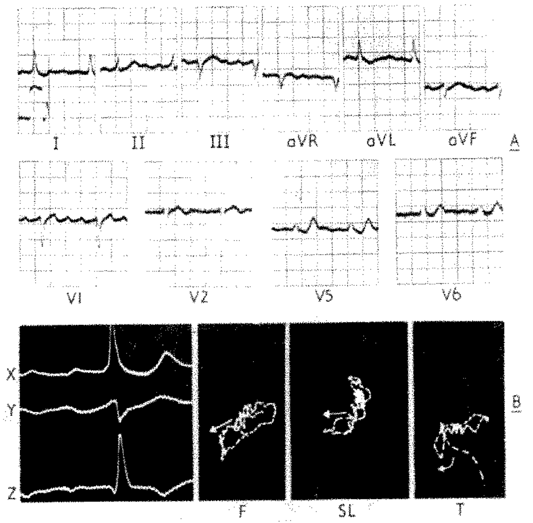

Fig. 6 *(A) Unusual example of 'uncommon' flutter. Electrocardiogram shows diphasic P waves in lateral and inferior leads at a rate of 330 per minute. The baseline has continuous undulation (Case 6). (B) Unusual example of 'uncommon' flutter. P loops are closed with the mean axis inferior to the left and anterior. Frontal plane axis +220°, left sagittal axis +129° (Case 6).*

'uncommon' flutter had three examples (50%) with a clockwise loop in the left sagittal plane (Table).

The 'uncommon' flutter loops are of great interest because of their general variety and individual conformity to description of supraventricular loci for arrhythmias. Three of the cases of 'uncommon' flutter had a normal P axis. Prinzmetal *et al.* (1952) noted that one form of 'uncommon' flutter had P waves similar to normal sinus P waves and occurred in 15 per cent of all cases of flutter. This form of atrial flutter theoretically might have a genesis in a rapid sinoatrial re-entrant mechanism (Childers *et al.*, 1973; Paulay *et al.*, 1973; Amat-y-Leon *et al.*, 1974; Narula, 1974; Wu *et al.*, 1975) or in a circuit which is primarily involving the so-called right internodal tracts (James, 1963; Hudson, 1970).

Two patients had a right axis P wave (Fig. 4B, 5B) one of which fulfilled electrocardiographic criteria of left atrial rhythm and had a P loop which was similar to constructs of left atrial P vectors. One patient with 'common' flutter had left atrial appendage stimulation postoperatively after mitral valve replacement (Fig. 7A, 7B). During left atrial pacing, lead V1 did not have a dome-dart configuration. However, the electrocardiogram and P loop satisfied recently advanced criteria for left atrial excitation (Mirowski and Alkan, 1967; Lau *et al.*, 1970; Mirowski *et al.*, 1970). The P loop was oriented to the right, inferior and anterior.

The distinctly unusual case of 'uncommon' flutter (Fig. 6A, 6B) had a rapid rate and an undulating baseline. The loop appeared to close and to have an almost equal right-left, superior-inferior, and anterior-posterior orientation. This pattern may correspond to the most infrequent of Prinzmetal's 'uncommon' flutter categories—the sine wave group (Prinzmetal *et al.*, 1952).

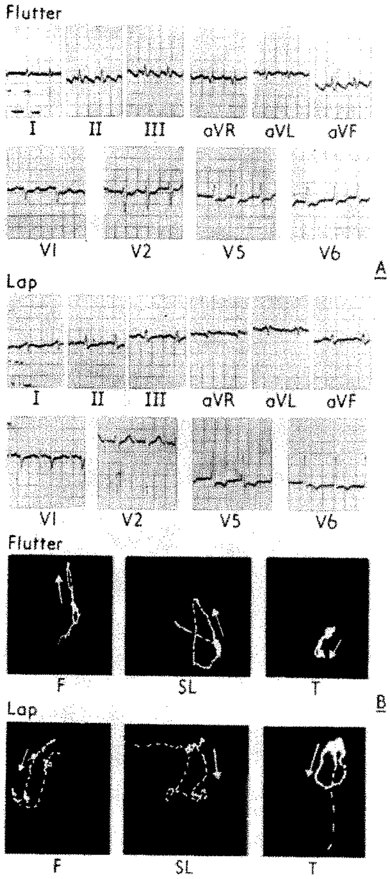

Fig. 7 *(A) Examples of 'common' flutter and left atrial pacing in the same patient. Top panel: electrocardiographic pattern of 'common' atrial flutter. Bottom panel: left atrial appendage pacing 8 days after operation for mitral valve replacement. P waves are negative in I, aVL, and V6. Lead V1 does not have dome-dart P (Case 21). (B) P loops of 'common' flutter and left atrial pacing in the same patient. Top panel: flutter P loop is oriented caudad-cephalad, slightly to the left and anterior. Bottom panel: left atrial appendage pacing results in P loop which is oriented inferior, to the right, and anterior (Case 21).*

It has been stated that electrocardiographic analysis and P loop vectorcardiography cannot resolve the mechanism of flutter (Scherf and Schott, 1973). Based upon experimental evidence it is generally accepted that P loops can be inscribed by macrocircuit atrial pathway or by a focus of excited atrium. In fact, experimental and clinical studies of the mechanism of flutter have found evidence for both a circus movement and focal atrial excitation in the same study (Giraud *et al.*, 1955; Kato *et al.*, 1956; Marques *et al.*, 1962; Kishon and Smith, 1969). Macrocircuits have been suggested to explain a variety of supraventricular (Amat-y-Leon *et al.*, 1974; Narula, 1974) as well as ventricular arrhythmias (Wellens *et al.*, 1972; Spurrell *et al.*, 1973; Wellens *et al.*, 1974). The specialised conductive pathways within the atria were described in part by Wenckebach (1908), Thorel (1910), and Bachmann (1916). In 1922 Rothberger-Wein, one of the first proponents of a focal theory commented on Lewis' work as follows: 'It still remains that the theory of the circus movement has some theoretical difficulties. Why should a wave return to its origin? Thorel has described a conductive path, but what about the return path?' In 1963, James described several routes for excitation to travel from the sino-atrial node to the atrioventricular node and vice versa. He also carefully delineated the possible combinations of internodal circuits. In spite of James' clear presentation, this concept is not completely established, and a recent review concluded that the evidence did not firmly support the existence of specialised inernodal pathways (Janse and Anderson, 1974).

Our data are compatible with several mechanisms of flutter. 'Common' flutter could originate from a preferred continuous circuit of excitation or alternatively could originate from an area of focal excitation or re-entry at the coronary sinus or AV junction. Focal excitation or re-entry in these areas may be associated with or be independent of a preferred circuit of excitation. 'Uncommon' flutter may represent a variety of unusual circuits or a variety of unusual supraventricular pacemaker tissues (Amat-y-Leon *et al.*, 1974) in association with or independent of nonpreferred atrial circuits of excitation. Perhaps subgroups could be identified through analysis of flutter loops which, when subjected to electrophysiological interventions (Wellens, 1971) would differ in mode of onset, maintenance, and termination.

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Initial care of hypertensive patients

Influence of different types of clinical records

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The initial record of history and clinical findings has been studied in 278 patients attending three hypertension clinics. Half of these were randomly allocated to standard case notes and the other half to a special structured questionnaire record. The investigations carried out in a total of 521 patients with raised arterial pressures were examined.

The records derived from the structured questionnaire were much more complete than the standard case notes but the difference was less obvious for a positive record than a negative one. None of the investigations was carried out in all patients, even though it was the policy of the clinics that most of them should be. A possible aetiological diagnosis was made in 28 patients and, at the time of writing, 3 patients had benefited from a surgical operation carried out as a result of investigation. These results raise the question of the quality of the initial care of hypertensive patients and suggest that the structured questionnaires might lead to an improvement. It remains to be established whether all the information collected does influence the outcome in patients with hypertension.

High arterial pressure is one of the few chronic conditions that is amenable to long-term medical treatment (Veterans Administration Co-operative Study 1967, 1970). It is fairly widely agreed what historical and clinical features and investigations are necessary information for the proper management of patients with high blood pressure. A previously published paper by Frohlich and his associates (1971) showed that the recording of these initial features was very incomplete in a group of hospitals in Oklahoma City including the University Hospital. The present study was undertaken as part of a larger one to improve record keeping and patient care in the hypertension clinics of three hospitals. It has provided the opportunity to carry out a controlled trial of the effect of different types of record system on the collection of clinical information and to consider the value of the information derived from investigations.

Methods

Hypertension clinics at three University hospitals, the Radcliffe Infirmary in Oxford, and Hammersmith, and King's College Hospitals in London, co-operated in the present study. Each was allocated a quota of patients to be included in the study and during the period of recruitment all newly referred hypertensive patients were admitted to it. They were allocated by randomisation either to standard hospital charts or to a structured questionnaire. A description of the questionnaire has been published (Beilin *et al.*, 1974) as have some of the details of the trial (Bulpitt *et al.*, 1976). The number of patients and some clinical details of them are shown in Table 1.

The identity of the patients allocated to standard hospital records was recorded at the time of randomisation, but no further action was taken concerning them until a year later when the charts were drawn from the file and all the information in them concerning clinical history, family history, social history, and clinical signs and investigations was abstracted and coded. The study forms part of a larger one in which the use of a computer-based clinical record is compared with standard charts (Bulpitt *et al.*, 1976). However, the intervention of the computer is not relevant to the present comparison which is based solely upon the initial evaluation.

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Table 1 *Allocation of patients to standard records and structured questionnaire*

	Standard records 142	*Structured questionnaire 136*
Pulse rate beats/min	83·4	82·1
Lying diastolic blood pressure (mmHg)	106 4	105·2
Lying systolic blood pressure (mmHg)	177·4	177 8

The results in the case records were punched on to paper tape and analysed on an ICL 1903 computer (Coles *et al.*, 1976). For the present analysis a count was made of the number of charts containing a positive record of a particular feature, the number having a negative record, and the number of case records containing no record at all of that feature.

A proportion of the patients admitted to the trial turned out to have near normal blood pressure when they were seen at hospital. Detailed investigation of them may not have been appropriate and we have evaluated the investigations carried out in a larger sample of 521 patients for whom clinical information was recorded on the structured questionnaire and whose systolic pressure exceeded 140 mmHg and whose diastolic pressure was equal to or greater than 95 mmHg without treatment. In this part of the investigation a further search of laboratory records was made to try to ascertain the results of investigations recorded as ordered but where no results had been entered. To facilitate comparison, the data from our study have been classified using the same headings as those used in an earlier investigation in Oklahoma City (Frohlich *et al.*, 1971).

Results

HISTORY

The computer record derived from the structured questionnaire gave by far the most complete history of crucial features in hypertensive patients. An entry was present for each feature in nearly 100 per cent of the patients. The standard notes of the three participating clinics were less complete; on average 65·9 per cent of the items had a record of the feature concerned. The Oklahoma City records had an entry on an average of 31·9 per cent of these features, but these clinics were not specialist hypertension clinics (Table 2).

Positive features were recorded more frequently in the structured questionnaire (average 22·4%) than in the standard case notes (average 18·5%). The difference between the two systems was less for positive records than for the presence of any record. This suggests that information is more likely to be written down if it is positive than if it is negative.

Clinical signs

A record of key clinical signs was present in a higher proportion of the structured questionnaire records than the standard ones (77·5% and 62·7% respectively). It is noteworthy that though the records from the structured questionnaire were much more complete for the examination of the femoral pulses and abdominal bruits, none of the patients allocated to this type of record had any abnormality of these clinical signs detected (Table 3). This raises the question of what rate of significant abnormalities is required for a particular part of the clinical examination to be retained as a routine.

Investigations

The analysis of investigations done was derived from a larger sample than the data on history and clinical signs. None of the investigations had been carried out in all the patients. The highest proportion was 94·4 per cent for electrocardiogram.

Tests for phaeochromocytoma (45·7%), a urine culture (64·7%), and an intravenous pyelogram (67%) were done less often. These figures are disconcerting as it was policy in two of the three

Table 2 *History*

	*Computer record**		*Standard record**		*Oklahoma City study*
	Present	*Positive*	*Present*	*Positive*	
Family history of hypertension	86 8	28 7	62 0	21 8	28
Statement on CNS symptoms	100 0	37·5	58·5	18 3	24
History of angina pectoris	99 3	10·3	77 5	7 7	63
History of exertional dyspnoea	99 3	37 5	83·8	30·3	43
History of oedema	97 8	19 1	46 5	10 6	38
Statement on other cardiovascular symptoms	99 3	2 9	38 0	1 4	23
Statement on genitourinary symptoms	100 0	43 4	86 6	38 7	31
History of dysuria	100 0	9·6	79 6	7·0	25
History of haematuria	99 3	2·2	54 2	4 9	19
History of nocturia	99 3	39·7	72·5	34 5	25

*Percentage of all records with any comment present and with a positive statement made.

Table 3 *Clinical signs*

	*Computer record**		*Standard record**		*Oklahoma City study*
	Present	*Abnormal*	*Present*	*Abnormal*	*Present*
Description of optic fundi	98·5	71·3	94·4	55·6	65
Description of neck veins	97·1	2·9	81·0	1·4	20
Description of lung findings	96·3	6·6	91·5	7·7	89
Description of thyroid size	0·7	0·7	9·9	2·8	63
Description of cervical bruit	94·9	0·7	30·3	0·7	20
Estimate of cardiac size	81·6	0·0	66·9	0·0	69
Presence of extra heart sounds	98·5	6·6	88·7	7·7	9
Note on cardiac rate	91·9	—	76·8	—	75
Note on cardiac rhythm	91·9	—	78·2	—	77
Ankle oedema	99·3	2·2	42·2	3·5	58
Femoral pulse	100·0	0·0	67·6	0·0	9
Abdominal bruit	75	0·0	35·2	0·7	14

*Percentage of all records with any comment present and an abnormality detected.

Table 4 *Investigations*

Investigations	*Computer record**	*Oklahoma city**
Urine analysis	93·1	96
Complete blood count	33·0	99
Blood glucose	69·5	17
Plasma sodium	91·2	51
Plasma potassium	91·0	51
Plasma urea	92·7	—
Chest radiograph	87·3	86
Electrocardiogram	94·4	88
Test for phaeochromocytoma	45·7	11
Urine culture	64·7	20
Intravenous pyelogram	67·0	34
Renal arteriogram	0·8	6

*Percentage of cases in which each investigation was carried out.

clinics that these tests should be done in all new referrals (Table 4).

The low figure for complete blood count must be interpreted with caution for 78·3 per cent of patients had a haemoglobin estimation without a full blood count.

The cost and inconvenience of investigation in hypertensive patients can only be justified if there is a yield of positive information that leads to improvements in patient care. In terms of aetiological factors the results of investigating 521 patients shown in Table 5. Five patients were thought to have a renal artery stenosis on the basis of the intravenous urogram but this was disproved in two by renal angiography. Of the three in whom the diagnosis was confirmed, one is awaiting surgery, one had extensive irradiation of para-aortic lymph nodes for a seminoma and eventually died of volvulus and intestinal obstruction, and the third had extensive atheromatous disease and was not considered suitable for surgery. One patient who presented with hypercalcaemia and renal stones had a parathyroidectomy to avoid further renal damage; his mild hypertension was controlled by diuretics and was not the main problem.

Table 5 *Possible aetiological diagnoses in 521 hypertensive patients*

Phaeochromocytoma	1
Renal artery stenosis	3
Polycystic kidneys	2
Retroperitoneal fibrosis	1
Renal papillary necrosis	1
Chronic pyelonephritis	16
Cushing's syndrome	1
Acromegaly	1
Primary hyperparathyroidism	1
Disseminated lupus erythematosis	1

Twelve patients had a significant growth of pathogens in a urine culture (Table 6). Though a positive culture was 3·4 times as common in patients who gave a history of dysuria, two-thirds of the positive tests were in patients without a history of dysuria. Treatment of these infections did not affect the blood pressure and it is not possible to say whether it may have influenced the long-term prospects for renal function.

The blood urea was less than 40 mg/100 ml (6·64 mmol/l) in 372 patients, between 40 and 60 mg/100 ml (6·64 and 9·96 mmol/l) in 105, and over 60 mg/100 ml (9·96 mmol/l) in 30 patients. Knowledge of the raised blood urea in these 30 patients was thought to have altered management in that it influenced the choice of drug, the decision about other investigations, and advice about prognosis.

Other diagnoses were made in the patients, e.g.

Table 6 *Result of urine culture in 379 hypertensive patients*

	No dysuria	*Dysuria*	*Total*
Urine culture negative	320	47	367
Urine culture positive	8	4	12
Total	328	51	379
Percentage positive	2·5%	8·5%	3·3%

11 patients were found to have small renal calculi on the IVU but though these affected management they did not lead to procedures that might have cured the hypertension.

Discussion

This study raises two important questions. The first concerns the quality of initial care of hypertensive patients and asks why many of the patients attending these specialist clinics had an incomplete record of features that most doctors would regard as important. Specialist hypertension clinics should obtain a more complete record than general medical clinics such as those studied in Oklahoma City. Few of the items obtained a 100 per cent score, though the structured questionnaire was close to it on most of the historical items and many of the clinical features. Obviously a well-designed questionnaire is a better way of obtaining a complete record than relying on the physician's recall of a similar series of questions in his mind. However, the questionnaire was not infallible and recording fell to 75 or 80 per cent for items such as heart size and abdominal bruit despite provision of a preprinted box for the information to be entered. The incomplete investigation of the patients is also somewhat disturbing. Why had less than 100 per cent of patients had an electrocardiogram or a plasma potassium estimation? There are probably many reasons: some tests may have been done but the results lost, samples may have gone astray, patients failed to attend for investigations, or doctors forgot to order them. Achievement of a complete record evidently requires constant checking that results of investigations have been entered. One advantage of a computer-based system is that such checking can be done relatively easily. It is of interest that the VMA was measured in only just under half of the patients; this investigation was not preprinted on the check list at the end of the structured questionnaire, whereas all the others were.

Use of a structured questionnaire for a specific disease entity such as hypertension is most practicable in a specialist environment where the diagnosis has already been correctly made in the majority of patients before they are given appointments. Thus, our system in its present form is appropriate to a hypertension clinic but may be difficult to implement in a general medical clinic or family practice, though one general practitioner has entered over 100 patients on the system.

The second question is whether it made any difference to management whether the information was collected or not. Would the quality of care have been better if every item had scored 100 per cent? Might a better system just lead to more unnecessary intravenous pyelograms being carried out? Judged purely on the yield of positive information, the history seems to be the most fruitful source of abnormal findings while the clinical examination gave much less positive information in these patients, most of whom had slightly raised blood pressure.

Could most of the clinical examination and investigations be discarded? Many have questioned the value of the routine intravenous pyelogram in hypertensive patients, and we have been engaged with other colleagues in an attempt to redefine the selection criteria in order to reduce the number greatly and improve the proportion of positive tests (Lewis *et al.*, 1976). It is a difficult question to decide what yield of positive information differentiates between a worth-while test and one that ought to be discarded. To the individual patient who has a phaeochromocytoma it is a life-and-death matter that it should be detected and removed. But the hundreds of patients who collect negative 24-hour urine samples and those who pay for them might well have a different view. To investigate this question poses difficulties, but it is inevitable that those who define quality by studying the process of medical care must ultimately be asked to justify the cost effectiveness of individual components that they judge to make up optimal health care of a particular condition.

We are at present using a simpler structured questionnaire which is intended for use in family practice. It is our intention then to examine in hospital the effects upon patient care of using this in place of the present one.

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Long-term prognosis after acute anterior infarction with atrioventricular block

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The purpose of this study was to evaluate the need for permanent pacing in patients who have survived the effects of anterior myocardial infarction with complete heart block and have returned to sinus rhythm but who are left with impairment of intraventricular conduction. We have reviewed 52 patients with complete heart block complicating recent anterior myocardial infarction. Temporary pacing was instituted in all patients. There were 25 hospital survivors who were followed for an average of 49 months. Long-term pacing was established in 4 patients. Of the 21 patients in sinus rhythm, 14 had partial bilateral bundle-branch block with either right bundle-branch block and left anterior hemiblock or right bundle-branch block and left posterior hemiblock; at the end of the follow-up period, 10 of these 14 were alive and well. Furthermore, permanent pacing failed to prevent sudden death in 2 patients. At the present time, therefore, we conclude that long-term pacing is not justified in patients, otherwise asymptomatic, with partial bilateral bundle-branch block persisting after transient complete heart block in anterior myocardial infarction.

Survivors from acute anterior infarction complicated by complete heart block usually return to sinus rhythm after a few days, but most are left with electrocardiographic evidence of bifascicular block, sometimes with additional prolongation of the PR interval. In view of the fact that atrioventricular conduction may be precarious and that coronary disease is by nature progressive, there is a case for installation of a demand pacing system. On the other hand, competition or excessive power of stimulation could produce fatal ventricular fibrillation. Furthermore, endocardial potentials necessary for appropriate function of the demand pacemaker may be reduced in these patients who have almost invariably had a very large infarct. For this reason, we have been reluctant to use a pacemaker in such cases and now give the results of a follow-up averaging 49 months in a group of 25 patients.

Methods

The medical records and standard 12-lead electrocardiograms of 52 patients admitted to our care in the 10-year period up to December 1973 were reviewed. All had been referred with recent anterior myocardial infarction complicated by the development of complete heart block. It was not known whether there was pre-existing fascicular block before infarction. In 2 patients (Cases 3 and 6) a narrow QRS in the presence of complete heart block suggested proximal atrioventricular block. In all other patients the level of the block was considered to be distal in site because of the slow rate of the escape pacemaker and a QRS width of at least 0·12 s. All patients needed temporary pacing.

The diagnosis of acute myocardial infarction was established by a typical history accompanied by characteristic enzyme rises and the development of pathological Q waves accompanied by ST segment and T wave changes in the anterior chest leads. Bundle-branch block was defined according to the criteria of Goldman (1967) and the criteria for hemiblock were those of Rosenbaum (1970). Partial bilateral bundle-branch block was defined as right bundle-branch block and left anterior hemiblock or right bundle-branch block and left posterior hemiblock.

The usual hospital stay was at least 3 weeks and follow-up observations were obtained in all patients. His bundle electrograms were recorded in 8 patients after return to sinus rhythm, using the technique described by Scherlag *et al.* (1969).

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Results

Of the 52 patients 27 died in hospital, giving a mortality of 52 per cent. The majority of deaths in hospital were the result of myocardial failure. Four patients developed ventricular fibrillation despite pacing, 1 patient had a further infarct, and 1 patient who had returned to sinus rhythm with right bundle-branch block and left anterior hemiblock within 24 hours of infarction died suddenly 2 weeks after admission (Table 1).

Table 1 *Initial outcome in 52 patients with acute anterior myocardial infarction with complete heart block*

Deaths in hospital		27
Myocardial failure	21	
Ventricular fibrillation	4	
Further infarction	1	
Sudden death	1	
Survivors		25
Atrioventricular block (paced)	1	
Sinus rhythm (1 paced)	24	

The 25 survivors, with ages ranging from 36 to 78 years (mean 60 years), who left hospital have been followed to death or for a period of time ranging from 21 to 84 months and averaging 49 months. Only 1 of the 25 survivors (Case 25, Table 2) was still in complete heart block when ready for discharge from hospital and indisputably required a permanent pacing system. Of the 24 who had returned to sinus rhythm only 2 had a normal PR interval and a normal QRS complex (Cases 1 and 2). In 5 patients there was both prolongation of the PR interval (more than 0·20 s) and of the QRS complex with partial bilateral bundle-branch block, indicat- the possibility of return to complete heart block. In 2 of these patients (Cases 14 and 19) an attempt was made to install a permanent demand pacing system but, because endocardial potentials were considered too low, it was thought safer not to pace them; both are still in sinus rhythm 47 and 49 months later. In a third patient (Case 20), with normal endocardial potentials, the continued use of procainamide for ectopic beats in the presence of partial bilateral bundle-branch block led us to install a demand pacing system, but despite this he died suddenly 18 months later. In 2 patients, complete heart block without syncopal attacks developed 4 months and 24 months later and pacemakers were inserted; 1 of these (Case 3) had had a long PR interval and a normal QRS and was well at 53 months, but the other (Case 5) who had had a long PR interval, left bundle-branch block, and heart failure, died suddenly at 3 years.

Thus, of the 16 patients alive and well at the end of the follow-up period, only 2 with complete heart block were being paced. The remainder were in sinus rhythm; 10 had partial bilateral bundle-

Table 2 *Electrocardiographic findings after recovery from infarction and follow-up in the 25 survivors*

Case No.	*Age and sex*	*PR interval (s)*	*QRS*	*HV (s)*	*Follow-up period (mth)*	*Outcome*
1	63 M	0·16	Normal	—	84	Sinus rhythm; alive
2	49 M	0·18	Normal	—	71	Sinus rhythm; alive
3	68 M	0·26	Normal	—	53	CHB; paced; alive
4	71 F	0·18	LBBB	—	3	Sinus rhythm; death
5	65 M	0·22	LBBB	—	36	CHB, paced; sudden death
6	57 M	0·28	LAH	—	43	Sinus rhythm; death
7	55 F	0·14	LAH	—	38	Sinus rhythm; sudden death
8	66 M	0·14	LPH	—	39	Sinus rhythm; alive
9	61 M	0·18	RBBB	—	55	Sinus rhythm; alive
10	65 M	0·16	RBBB+LAH	0·045	65	Sinus rhythm; alive
11	64 M	0·14	RBBB+LAH	0·040	13	Sinus rhythm; sudden death
12	48 M	0·16	RBBB+LAH	—	31	Sinus rhythm; alive
13	78 F	0·16	RBBB+LAH	—	36	Sinus rhythm; alive
14	59 M	0·21	RBBB+LAH	0·070	47	Sinus rhythm; alive
15	64 M	0·16	RBBB+LAH	—	62	Sinus rhythm; alive
16	61 F	0·12	RBBB+LAH	—	3	Sinus rhythm; death
17	47 M	0·20	RBBB+LAH	—	17	Sinus rhythm; death
18	69 M	0·20	RBBB+LAH	0·070	23	Sinus rhythm; alive
19	66 M	0·24	RBBB+LAH	0·070	49	Sinus rhythm; alive
20	71 M	0·24*	RBBB+LAH	0·065	18	Sinus rhythm; paced; sudden death
21	56 M	0·21	RBBB+LPH	0·065	55	Sinus rhythm; alive
22	60 M	0·16	RBBB+LPH	0·040	21	Sinus rhythm; alive
23	69 M	0·14	RBBB+LPH	—	41	Sinus rhythm; alive
24	36 M	0·22	RBBB+LPH	—	34	Sinus rhythm; sudden death
25	59 M	CHB*	LBBB	—	57	CHB; paced; alive

LBBB, left bundle-branch block; LAH, left anterior hemiblock; LPH, left posterior hemiblock; RBBB, right bundle-branch block; CHB, complete heart block.
*Patients paced before discharge from hospital.

branch block, and 3 of these also had a prolonged PR interval.

Of the 9 late deaths (Table 3), 4 were attributable to chronic irreversible heart failure or further infarction. The other 5 were sudden and might have been caused by ventricular standstill. Of the 5, 2 had pacemakers and normal *in vivo* function of the pacemaker had been confirmed in both patients within 2 months of death; furthermore, both the pacing electrode and pulse generator were satisfactory at necropsy. There were 3 patients who might have benefited from a pacemaker: 1 (Case 24) was in chronic heart failure, but in the 2 others a pacemaker might have been life-saving. Selection of these patients for prophylactic pacing would have presented difficulties since one (Case 7) was in sinus rhythm with unifascicular block, and the other (Case 11) was in steady sinus rhythm with a PR of 0·14 s and an HV of 0·04 s, though he did have right bundle-branch block with left axis deviation.

Discussion

The mortality of acute anterior infarction with complete atrioventricular block is reported to be approximately 30 per cent and results from the large size of an infarct, large enough to involve both right and left bundle-branch conducting systems (Stock, 1969; Norris *et al.*, 1972). The lower mortality (52%) in the group reported here may be the result of some selection of cases by their ability to survive transfer from another hospital. On the other hand, special precautions taken with the pacing technique probably played an important part, as these patients are particularly vulnerable to arrhythmias. Suppressant drugs were given before the electrode was passed through the tricuspid valve and a close watch was maintained for the low endocardial potentials which are likely to occur in these patients with large infarcts and heart failure, and which may result in failure of inhibition of the demand pacing system, causing inappropriate stimulation with its danger of ventricular fibrillation (Chatterjee *et al.*, 1969). Thresholds were measured daily and the pacing voltage was kept to less than twice the threshold voltage. In some borderline cases overdrive fixed rate pacing was preferred to demand pacing. Demand pacing systems were not withdrawn until 7 days after return to sinus rhythm with the final 24 hours on a pacing counter to detect transient return of block. Despite these precautions, 4 patients died unexpectedly of ventricular fibrillation late in their hospital stay.

The long-term follow-up in this series confirms the high late mortality in survivors from complete heart block complicating anterior myocardial infarction. Sudden death, however, occurred in only 2 of the 14 non-paced patients with partial bilateral bundle-branch block, and our experience contrasts with that of Atkins and colleagues who reported sudden death within 6 months of hospital discharge in 5 of 6 unpaced patients who had partial bilateral bundle-branch block after anterior infarction with transient complete heart block (Atkins *et al.*, 1973). It is interesting to note that the same authors also reported a group of 12 patients in sinus rhythm with right bundle-branch block and left anterior hemiblock who were permanently paced; 6 died (2 suddenly) within 15 months (Ritter *et al.*, 1975).

A review of the published reports shows that the persistence of conduction defects after acute myocardial infarction is not a reliable guide to the risk of late sudden death. In the Coronary Drug Project, 13 patients with partial bilateral bundle-branch block after myocardial infarction were followed for

Table 3 *Electrocardiographic findings in 9 patients dying after discharge from hospital*

Case No.	*PR interval*	*Type of conduction abnormality*	*Interval between infarct and death (mth)*	*Other features*
Sudden death				
5	0·22	LBBB→CHB Permanent pacing	36	Dizziness + heart failure before pacing
7	0 14	LAH	38	Symptom free
11	0·14	RBBB + LAH (HV 40 ms)	13	Symptom free
20	0·24	RBBB + LAH (HV 65 ms) Antiarrhythmic therapy Permanent pacing	18	Necropsy showed fresh occlusion of right coronary artery
24	0·22	RBBB + LPH	34	Heart failure
Further infarct				
16	0·12	RBBB + LAH	3	
Heart failure				
4	0·18	LBBB	3	
6	0 28	LAH	43	
17	0·20	RBBB + LAH	17	

a period of 3 years without mortality (Coronary Drug Project Research Group, 1972). Nimetz *et al.* (1973) reviewed a group of 71 patients with right or left bundle-branch block complicating acute myocardial infarction and found that the presence or absence of atrioventricular block failed to distinguish candidates for late sudden death: in 30 patients with associated second or third degree atrioventricular block there were 18 hospital and 3 late (2 sudden) deaths; by contrast, in the 41 patients without atrioventricular block there were 5 hospital and 14 late deaths (8 sudden) (Nimetz *et al.*, 1973). More recently, Rosen and his colleagues recorded intracardiac electrocardiograms in a large but heterogeneous group of patients with right bundle-branch block and left anterior hemiblock and found no significant difference in the incidence of sudden death between those with prolongation of the HV interval and those in whom this measurement was normal (Denes *et al.*, 1975).

The mechanism of sudden death in such cases remains speculative. It has been implied that patients with partial bilateral bundle-branch block are at risk from death as a result of complete heart block and asystole. Such patients, however, have advanced coronary artery disease and sudden death may well be the result of ventricular fibrillation during an ischaemic attack. Watanabe has reported a high incidence of ventricular arrhythmias in patients with intraventricular conduction defects (Watanabe *et al.*, 1973). Hasanain *et al* (1973) have reported that the majority of patients with bifascicular block have premature ventricular beats and occasional ventricular tachycardia when exercised on the treadmill. The fact that sudden death occurred in 2 of the 4 patients with permanent pacing systems in our series indicates the potential risk of ventricular fibrillation, possibly as a result of inappropriate stimulation by the pacemaker during acute myocardial ischaemia or infarction.

In conclusion, a high early and late mortality is to be expected after anterior infarction complicated by complete heart block because of the extent of coronary disease likely to be present and the large area of myocardial damage. It is doubtful, however, whether the overall late mortality is significantly different from that in any group of patients with severe coronary artery disease. It is, therefore, extremely difficult to judge the part played by irreversible damage to conducting tissue. From the evidence available we conclude that there is no justification at present for the routine insertion of a prophylactic pacing system in patients, otherwise asymptomatic, who have returned to reliable sinus rhythm after anterior myocardial infarction with complete heart block, even in those with persisting partial bilateral bundle-branch block.

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Formes frustes of Marfan's syndrome presenting with severe aortic regurgitation

Clinicogenetic study of 18 families

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Eighteen patients who presented with severe aortic regurgitation and dilatation of the ascending aorta were found to be formes frustes *of Marfan's syndrome and formed the basis for this clinicogenetic study. All had aortic valve replacement and reconstruction of part of the ascending aorta. The diagnosis was confirmed by histological examination of the aortic tissue.*

There were 126 first degree relatives; 85 were living and 67 (78·8%) of these were examined. Limited information was available about 32 of the 41 relatives who had died. No relative had the classical clinical features of Marfan's syndrome but stigmata of the disease were found in 25 (37·3%) of the 67 first degree relatives examined. In 21, the abnormality was confined to the cardiovascular system, the skeleton, or the eye, but in 4, abnormalities involved 2 systems.

Cardiovascular abnormalities affecting the aortic valve or aortic wall were present in 6 (9·0%) of the 67 first degree relatives examined. One or more of the skeletal indices measured (height-span difference, metacarpal index, phalangeal index) was abnormal in 18 (26·9%) and ocular abnormalities were found in 5 of 51 (9·8%) examined. There were no relatives with dislocation of the lens or iridodonesis.

Using strict diagnostic criteria, a minimum of 37·3 per cent of the first degree relatives examined were affected; this involved 12 of the 18 families studied. There was nothing in our data to suggest that the formes frustes *of the disease had a different mode of inheritance from the classical syndrome.*

The eponym, Marfan's syndrome is used to describe a genetically determined disorder of connective tissue affecting the skeleton, cardiovascular system, and eye. The clinical picture has evolved since the original account by Marfan (1896) when he used the name 'dolichosternomelia' to describe unusually long and slender extremities. The term 'arachnodactyly' was introduced later by Achard (1902) who also noted the familial incidence. Ocular abnormalities were described by Börger (1914) and Ormond and Williams (1924) but it was not until 1943 (Baer *et al.*) that the cardiovascular components of the syndrome were recognized.

Marfan's syndrome may be readily diagnosed when the classical features are present but *formes frustes* are difficult to detect and define. Here, a single abnormality may be present such as isolated aortic regurgitation or a dislocated ocular lens; or there may be several minor and occult defects, each of which is difficult to detect. This is particularly the case when minor abnormalities are confined to the skeletal system.

The present study was undertaken to determine the nature and frequency of the stigmata of Marfan's syndrome in first degree relatives of 18 propositi who were examples of the *formes frustes*, each presenting clinically with severe aortic regurgitation. The mode of inheritance in these families was also studied.

Subjects and methods

Eighteen patients with severe aortic regurgitation and varying degrees of dilatation of the ascending aorta seen at the National Heart Hospital and Hammersmith Hospital between November 1965

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and October 1972 form the basis of this study. All were examples of the *formes frustes* of Marfan's syndrome. In none was the aetiological diagnosis made before operation though it was suspected in 7. All had aortic valve replacement (Starr-Edwards prosthesis) and reconstruction of part of the ascending aorta with 'teflon' or 'dacron' grafts. The diagnosis of Marfan's syndrome was confirmed as a result of histological examination of the aortic tissue obtained at operation.

As in previous studies (Emanuel *et al.*, 1968, 1971, 1975), arrangements were made to interview the propositus or a close relative at home and a family pedigree was drawn up which included all first and second degree relatives and first cousins. Relevant information when available on more distant relatives was also recorded. During the interview, specific questions were asked to ascertain whether any relative was known to have abnormalities involving the heart, skeleton, or eye.

All the propositi who were alive and all first degree relatives who were willing to co-operate were examined at either the Middlesex Hospital, National Heart Hospital, or a convenient regional hospital. This involved a physical examination, chest radiographs (PA and lateral), an electrocardiogram, ophthalmological assessment, skeletal measurements of height and span, and the necessary radiographs for the calculation of the metacarpal index (MI) and the phalangeal index (PI). Phonocardiograms and echocardiograms were also carried out in those with questionable cardiovascular abnormalities.

Measurements of the height and span were considered abnormal if the span exceeded the height by 7·6 cm or 3 inches (Pearson and Lee, 1902; Sinclair *et al.*, 1960). The metacarpal index (the ratio between the total axial length of the second, third, fourth, and fifth metacarpals of the right hand and the total breadth of the same metacarpals at their mid points) was measured as described by Sinclair (1958) and Sinclair *et al.* (1960). A ratio of 8·4 or more was considered abnormal; doubtful values between 8·0 to 8·3 (Sinclair, 1958; McKusick, 1972) were excluded. The phalangeal index (the ratio of the length of the proximal phalanx of the right ring finger and its minimum width) was considered abnormal if in excess of 4·6 for men and 5·6 for women (Parish *et al.*, 1960). In order to decrease observer error, the metacarpal and phalangeal indices were calculated independently by 2 of us, and where differences existed after a second assessment, an average was taken.

The following skeletal features known to be associated with Marfan's syndrome were also noted but were not considered diagnostic: kyphoscoliosis, vertebral abnormalities, long ribs, clavicles, and toes, pectus excavatum, pectus carinatum, and the straight back syndrome (Twigg *et al.*, 1967).

Results

(a) PROPOSITI

Of the 18 propositi, 16 were men and 2 were women, their ages ranging from 28 to 61 years, with a mean of 44·7 years. The clinical features and operative details are summarised in Table 1.

Table 1 *Clinical and surgical data on the 18 propositi*

Pedigree no.	*Sex*	*Age (y)*	*Surgical findings* in addition to AR and dil. asc. ao.*	*Wt (kg)*	*Ht (cm)*	*Span (cm)*	*Ht-span difference (cm)*	*MI*	*PI*	*Ocular state*	*Date of op.*	*Date of death*
1:III.22	M	37	BAV, coarct.	62	171 5	180	−9 5†	8 0	4 6	NAD	25.6.70	19 12.74
2.III.12	M	28	BAV, coarct.	58	165	—	—	—	—	—	13.4.72	13 4 72
3:III.7	M	45	BAV	69 8	178	—	—	—	—	—	11.1.72	1 2.73
4:III.5	M	52	—	78·1	170	173	−3	7 0	4 3	NAD	2.12.70	Alive
5:III.6	M	47	—	63 4	176	—	—	—	—	—	8.2.66	2.8.73
6:III.7	M	61	ASOV	79·2	180	—	—	—	—	—	18 6 68	1.10.73
7:III.11	F	44	—	57·7	160	—	—	—	—	—	29.1.70	5 2.70
8:III.2	M	55	—	89 9	190	195 5	−5 5	7 0	4 4	NAD	2 6.71	Alive
9:III.13	M	38	—	93 7	167	180 3	−13 3†	7 0	4 3	NAD	12.11 65	Alive
10:III.19	F	49	—	83 5	158	156	+2	7 3	4·2	NAD	25.5.67	Alive
11:III 18	M	37	—	73 2	187	191	−4	—	—	NAD	16.2.70	Alive
12:III.2	M	33	ASOV	61 3	168·3	—	—	—	—	—	3.11.66	11.7 73
13:III.3	M	53	Aneu. des. ao.	75 3	167·5	177·8	−10·3†	7·5	—	NAD	26 10.72	30 1.75
14.III.2	M	48	—	74·7	183	—	—	9 0†	—	NAD	7.5.71	27 8 73
15:III.8	M	34	Diss. asc. ao., BAV	73·4	169	176·5	+2 5	7 4	3 9	NAD	22.4.70	Alive
16:III.2	M	55	BAV	83·9	179·8	190·5	−10·7†	7·5	4·5	NAD	3.3 72	Alive
17:III.10	M	45	—	83·7	160 5	168·3	−7·8†	6 3	3 8	NAD	8.12.70	Alive
18:III.7	M	45	MR	68·5	185·5	—	—	—	—	—	9.3.67	7.3.72

*All had aortic Starr valve replacement and 'teflon'/'dacron' grafts. †Stigma of Marfan's syndrome
AR, aortic regurgitation; Dil. asc. ao., dilated ascending aorta; MI, metacarpal index; PI, phalangeal index; BAV, bicuspid aortic valve; Coarct., coarctation of aorta; ASOV, aneurysm of sinus of Valsalva; Aneu. des. ao., aneurysm of descending aorta; Diss. asc. ao ; dissection of ascending aorta; MR, mitral regurgitation; NAD, nothing abnormal (pertaining to Marfan's syndrome) detected.

At the time this study started, 11 propositi were living and 7 were dead; 3 died during the study so that at the time of writing 8 were alive with a post-operative follow-up which varied from 3·4 to 9·8 years, with a mean of 5·5 years. Of the 10 who died, there were 2 operative deaths (within 1 month of operation) and 8 late deaths with an average survival of 4·3 years.

In addition to severe aortic regurgitation and varying degrees of dilatation of the ascending aorta, 5 of the propositi had a bicuspid aortic valve, 2 had aneurysms of the sinuses of Valsalva, and 2 had coarctation of the aorta; there was also a single example of each of the following: dissecting aneurysm of the ascending aorta, aneurysm of the abdominal aorta, and mitral regurgitation.

Information about the skeletal and ocular abnormalities among the propositi was incomplete. Limited skeletal data were available in 11. Height and span measurements were obtained in 10 and were abnormal in 5. The metacarpal index was measured in 10 and was abnormal in 1. The phalangeal index was measured in 8 and was normal in all. Thus, there was a single abnormal skeletal index in 6 of the 11 propositi examined.

The 11 propositi alive at the beginning of the study had a detailed ophthalmological assessment, and no ocular abnormality relevant to Marfan's syndrome was found (Table 1).

(b) FIRST DEGREE RELATIVES

In the 18 families, there were 126 first degree relatives (36 parents, 57 sibs, 33 children), 85 of whom were living and 67 (78·8%) of these were examined (4 parents, 34 sibs, and 29 children). Limited information was available on 32 of the 41 who had died. In 12 of the 18 families there was more than one affected member (Table 2).

One or more of the stigmata of Marfan's syndrome was present in 25 (37·3%) of the 67 living first degree relatives examined (3 parents, 10 sibs, and 12 children).

In 21 of these relatives, the abnormality was confined to the cardiovascular system, the skeleton, or the eye, but in 4, abnormalities involved two or more of these systems. None of the relatives examined had the classical features of Marfan's syndrome.

(*i*) *Cardiovascular abnormalities* (*Table* 2)

Abnormalities in the cardiovascular system compatible with Marfan's syndrome were found in 8 first degree relatives (6 living, 2 dead). Six showed dilatation of the ascending aorta on chest radiograph; 2 of these had additional aortic regurgitation and 1 a bicuspid aortic valve on clinical grounds. The seventh died from a dissecting aneurysm of the ascending aorta which was confirmed at necropsy and the eighth who was reported to have died from aortic regurgitation was a member of a family in which 3 more distant relatives had aortic aneurysms. Two of these 8 relatives had additional skeletal abnormalities (Table 2, Pedigree No. 13; III. 4, and IV.8).

In addition to these 8, there were 5 with cardiovascular signs of doubtful significance. Four had an isolated ejection murmur, either aortic or pulmonary, without a preceding ejection sound and one a late apical systolic murmur. All 5 had phonocardiograms and echocardiograms but in none was there confirmatory evidence of either bicuspid aortic valve or prolapse of the mitral valve. Investigations involving invasive techniques were considered unjustified. In 2 of these 5 relatives however, there were skeletal abnormalities compatible with Marfan's syndrome (Table 2 Pedigree No. 13, IV.7; Pedigree No. 17, III.13).

A further 3 first degree relatives had cardiovascular disease of uncertain aetiology, 2 had died and there was no necropsy, the third who was living and had cardiac failure refused detailed examination (see Fig, Pedigree Nos. 11:II.7; 15:II.6; 15:III.5).

(*ii*) *Skeletal abnormalities* (*Table* 2)

Sixty-seven first degree relatives had skeletal surveys. The height-span measurement was obtained in all 67 and was abnormal in 12 (17·9%). The metacarpal index and phalangeal index were measured in 53 relatives. The metacarpal index was abnormal in 9 (17·0%) and the phalangeal index in 5 (9·4%).

Eighteen first degree relatives showed one or more skeletal abnormality. A single abnormal skeletal index was present in 11 (height-span difference in 7; metacarpal index in 2; phalangeal index in 2), 2 abnormal indices were present in 6, and all 3 sketetal indices were abnormal in 1. Of these 18 relatives with skeletal abnormalities, 2 had associated cardiovascular abnormalities (Table 2 Pedigree No. 13: III.4, and IV.8) and a further 2 had ocular defects (Table 2, Pedigree No. 8:IV.3 and No. 13:IV 6). An additional 8 first degree relatives had a MI between 8·0 and 8·3, not in itself diagnostic, but as 2 had additional ocular abnormalities they were probably examples of Marfan's syndrome (Table 2, Pedigree No. 9:II.10, No. 16:IV.4).

Other less specific and less objective skeletal features found in 24 (35·8%) relatives included mild scoliosis in 8, unduly long slender ribs and clavicles in 6, long toes (especially the great toe) in 5, pectus excavatum in 3, and a straight back in 2.

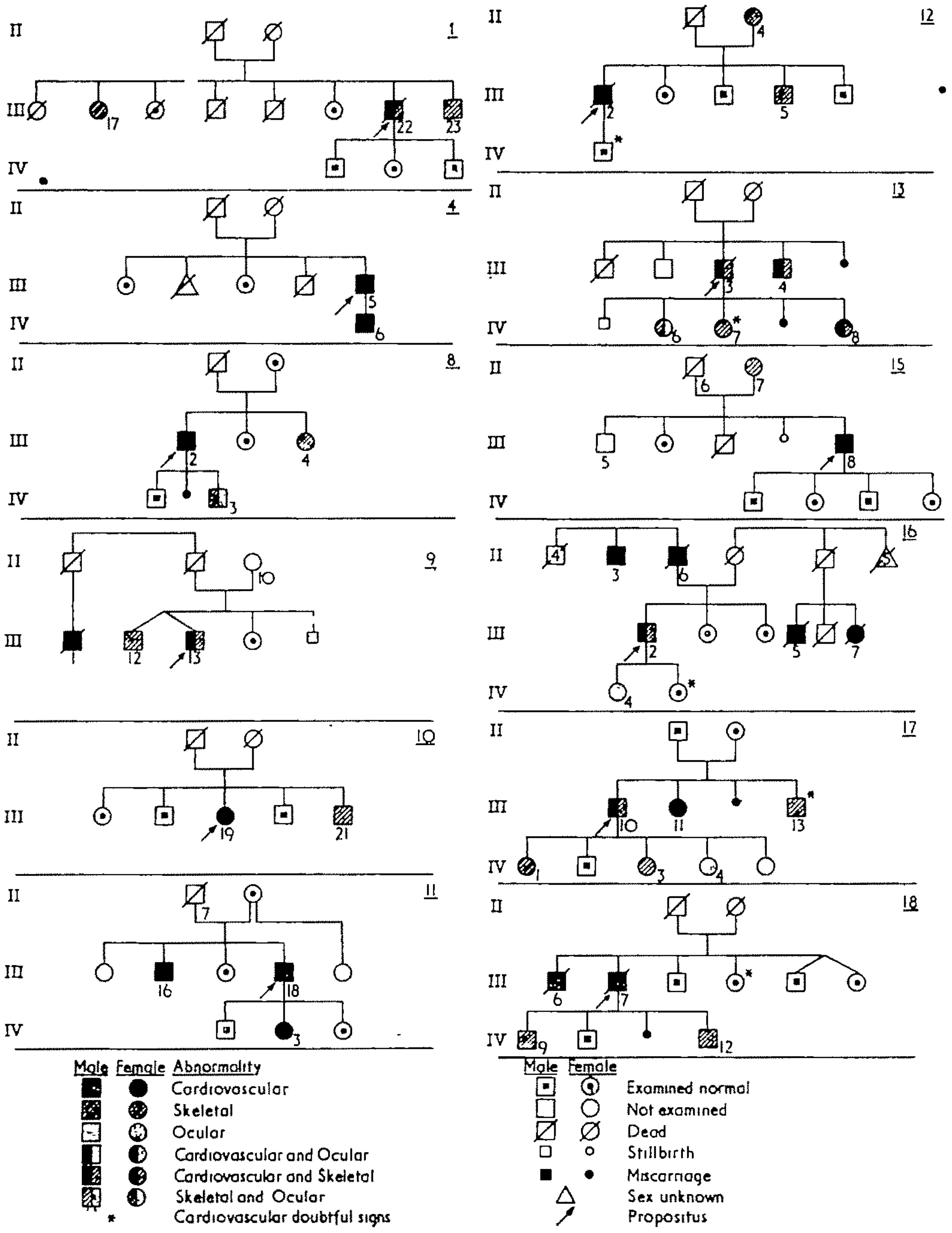

Fig. *Pedigrees of the first degree relatives in the 12 affected families. The numbering takes into account the existence of more distant relatives who have not been included in this study.*

(*iii*) *Ocular abnormalities* (*Table* 2)

A total of 51 first degree relatives had a detailed ophthalmological assessment by one of us (P.A. MacF.). Abnormalities compatible with Marfan's syndrome were found in 5 and included a single example of each of the following: spherophakia with severe myopia, hypoplasia of the iris, bilateral retinal detachment with severe myopia, bilateral cystoid degeneration, and peripheral retinal degeneration with myopia. Of these 5 cases, 2 had

Table 2 *Cardiovascular, skeletal, and ocular data on affected relatives*

				Musculoskeletal abnormalities							
Pedigree no.	*Sex*	*Age (y)*	*Cardiovascular abnormalities*	*Wt (kg)*	*Ht (cm)*	*Span (cm)*	*Ht-span difference*	*MI*	*PI*	*Additional abnormalities*	*Ocular abnormalities*
1:III.17	F	57	NAD	73·7	168·3	169	−0·7	8·5†	4·5	—	NAD
1:III.23	M	40	NAD	82·8	172	167·5	+4·5	7·4	4·8†	—	NAD
4:IV.6	M	24	Dil. asc. ao.†	61·6	169	167·8	+2·2	7·2	4·1	—	NAD
8:III.4	F	47	NAD	—	172	180	−8·0†	8·5†	5·7†	—	NAD
8:IV.3	M	18	NAD	62·7	181	187·5	−6·5	7·0	4·7†	Long first toe	Spherophakia†
9:II.10	F	70	NAD	88·4	158·8	164	−5·2	8·3	5·0	—	Bil. cyst. deg.†
9:III.12	M	46	NAD	72·6	170·3	185·5	−15·2†	7·0	4·2	—	NAD
9:III.1*	M	57	Rupt. abd. ao. an. (PM)†	—	—	—	—	—	—	—	—
10·III.21	M	51	NAD	77·4	174·8	183·5	−8·7†	—	—	—	NAD
11:III.16	M	46	Dil. asc. ao.†	—	165·3	165	+0·2	—	—	—	NAD
11:IV.3	F	19	Dil. asc. ao; AR†	—	177·3	175·3	+2·0	—	—	—	NAD
12:II.4	F	62	NAD	55·0	148·5	156·3	−7·8†	8·5†	5·0	—	NAD
12:III.5	M	29	NAD	67·1	172	179·8	−7·8†	7·8	4·1	—	NAD
13:III.4	M	52	Dil asc. ao.†	—	170·3	201	−30·7†	6·7	4·4	—	NAD
13:IV.5	F	25	NAD	72·2	165	172	−7·0	8·8†	5·4	Long toes and ribs, depressed sternum	Peri. ret. deg.†
13:IV.7	F	23	Ao. ESM	58·4	167·8	176·5	−8·7†	9·1†	5·4	Long toes and ribs	NAD
13:IV.8	F	17	Dil. asc. ao.†	76·1	148·5	156·3	−7·8†	8·8†	4·8	—	NAD
15:II.7	F	72	NAD	—	134·5	143·5	−9·0†	7·6	—	—	NAD
16:II.6	M	70	AR† (DC)	—	—	—	—	—	—	—	—
16:IV.4	F	28	NAD	62·3	173·5	177·8	−4·3	8·1	5·6	—	Bil. ret. det.†
16:II.3*	M	87	Abd. ao. aneu (resected)†	—	—	—	—	—	—	—	—
16:III.5*	M	62	Rupt. ao. arch an (PM)†	—	—	—	—	—	—	—	—
16.III.7*	F	67	Rupt. ao arch an (PM)†	—	—	—	—	—	—	—	—
17:III.11	F	40	Dil. asc. ao ; AR; BAV†	82·4	148·5	151	−2·5	7·6	4·4	—	NAD
17:III.13	M	36	Ao. ej. sy. murmur	73·1	162	177·3	−15·3†	6·9	4·1	—	NAD
17:IV.1	F	15	NAD	48·0	158·8	160	−1·2	9·0†	5·7†	—	NAD
17·IV.3	F	11	NAD	34·7	137·3	146	−8·7†	8·5†	4·9	Long ribs and clav.	NAD
17:IV.4	F	9	NAD	30·8	134·5	131	+3·5	7·5	4·0	—	Hypoplasia of iris†
18:III.6	M	45	Rupt. asc. ao. an. (PM)†	—	—	—	—	—	—	—	—
18·IV.9	M	28	NAD	67·9	186·8	199·5	−12·7†	7·7	—	Long toes, long flat chest	—
18:IV.12	M	14	NAD	46	166·5	171·5	−5·0	9·2†	5·1†	Long toes, long flat chest	NAD

General: MI, metacarpal index; PI, phalangeal index; NAD, nothing abnormal (pertaining to Marfan's syndrome) detected; ( ), dead relative; *second or third degree relative; otherwise first degree; †stigma of Marfan's syndrome; clav., clavicles.

Cardiovascular: Dil. asc. ao., dilated ascending aorta; Rupt. abd. ao. an., ruptured abdominal aortic aneurysm; AR, aortic regurgitation; Ao. ESM, aortic ejection systolic murmur; Rupt. ao. arch an., ruptured aortic arch aneurysm; PM, post mortem; DC, death certificate; BAV, bicuspid aortic valve.

Ocular: Bil. cyst. deg., bilateral cystoid degeneration of retina; peri. ret. deg., peripheral retinal degeneration; Bil. ret det, bilateral retinal detachment.

additional cardiovascular or skeletal abnormalities (Table 2 Pedigree No. 8:IV.3; and No. 13:IV.6).

A further 17 had ocular defects that were not specifically related to Marfan's syndrome, such as simple refractive errors, cataracts (congenital and acquired), and fundal abnormalities. Two of these relatives had scattered dot opacities in their lenses. There were no relatives with dislocation of the lens or iridodonesis.

(C) SECOND AND THIRD DEGREE RELATIVES (TABLE 2)

Information about these more distant relatives was fragmentary, but 4 were considered to have cardiovascular evidence of Marfan's syndrome. Three died of ruptured aneurysms (2 dissecting aneurysms of ascending aorta, 1 ruptured descending aorta), and all had necropsies. The fourth had an abdominal aortic aneurysm and was treated surgically.

Discussion

The term *formes frustes* implies that either all the classical features which include abnormalities of the skeleton, cardiovascular system, and eye are not present, or if they are, they are in a minor or subtle form not easily detected. The term is, therefore, imprecise and to some extent dependent on the awareness of the clinician who uses it. Some authors have confined the diagnosis of Marfan's syndrome to patients with 2 or more of the classical features (Wilner and Finby, 1964; Hirst and Gore, 1973). Bowers (1969) considered that the manifestations of Marfan's syndrome could be divided into major and minor features, the former being disorders of the ocular lens and a positive family history and the latter skeletal stigmata, cardiovascular abnormalities, and an increased excretion of urinary hydroxyproline. He restricted the term Marfan's syndrome to those patients who had at least one major and one minor manifestation of the disease.

Cardiovascular manifestations of the *formes frustes* are commonly aortic regurgitation with or without dilatation or dissection of the ascending aorta. Less common cardiovascular abnormalities include coarctation of the aorta (Eldridge, 1964b), dilatation or aneurysm of the sinuses of Valsalva (Tobin *et al.*, 1947; Steinberg *et al.*, 1957; Papaioannou *et al.*, 1961), bicuspid aortic valve (Soman *et al.*, 1974), abnormalities of the mitral and tricuspid valves (Shankar *et al.*, 1967; McKusick, 1972), including the floppy valve syndrome (Read *et al.*, 1965; Sherman *et al.*, 1970; McKusick, 1972; 1976), and the systolic click-late systolic murmur syndrome (Salomon *et al.*, 1975; Bon Tempo *et al.*, 1975). Atrial and ventricular septal defects (Ellis, 1940; Tolbert and Birchall, 1956), persistent ductus arteriosus (Anderson and Pratt-Thomas, 1953), Fallot's tetralogy (McKusick, 1955), aneurysm of the pulmonary artery (Lillian, 1949; Simon *et al.*, 1965), and coronary artery involvement (Becker and Van Mantgem, 1975) have also been described. The frequency of bicuspid aortic valve in Marfan's disease is unknown, which is in part because of the difficulty in making a clinical diagnosis even after angiocardiography and echocardiography (Feizi and Ruzic, 1976). In this series, 5 of the 18 propositi (27·8%) had a bicuspid valve, an unusually high incidence which may well reflect the mode of selection of the propositi, for all had severe aortic regurgitation requiring surgery, thus allowing inspection of the aortic valve in each case.

The practical importance of recognizing Marfan's syndrome presenting with isolated aortic regurgitation is threefold. First, progressive dilatation of the ascending aorta with or without dissection is common whereas it is rare in aortic regurgitation from other causes. Secondly, if aortic valve replacement is required, there are special hazards relating to the lack of connective tissue support; these include excessive haemorrhage, rupture of the aortic suture lines and secondary dehiscence of the inserted valve (Symbas *et al.*, 1970; Nasrallah *et al.*, 1975). Thirdly, it has been suggested that propranolol (Halpern *et al.*, 1971; McKusick, 1976) or reserpine (Wheat *et al.*, 1965; Murdoch *et al.*, 1972), if used sufficiently early, may delay progressive dilatation of the aortic root. In cases of aortic regurgitation of doubtful aetiology, measurement of simple skeletal indices such as height span difference, metacarpal and phalangeal indices, and an ophthalmic examination may be helpful and lead to the correct aetiological diagnosis. This was done retrospectively in 11 of the propositi after the diagnosis had been confirmed from histological examination of the aorta, and in 6 (54·5%) one of the skeletal indices was abnormal but none had ocular defects. Early recognition of the correct diagnosis may also be important when the skeleton is involved, for McKusick (1972) has raised the possibility of initiating puberty early in girls with oestrogen-progesterone treatment in order to control adult height and minimize the risk of severe scoliosis in later life.

None of the propositi or affected first degree relatives had the classical musculoskeletal features of Marfan's syndrome which again emphasizes the importance of looking for the less obvious stigmata and, if possible, establishing an objective method of measuring them. Skeletal indices are prone to observer error, which is minimized when measurements are obtained from radiographs, as with the metacarpal and phalangeal indices: the former is probably the most reliable skeletal index (Eldridge, 1964a) particularly if the stricter criteria of ratios in excess of 8·4 are used. Parish *et al.* (1960) however considered the phalangeal index more specific, but this is not universally accepted (Eldridge, 1964a; McKusick, 1972). Direct clinical measurements of the height, span, and upper and lower body segments are more subjective; this is particularly so in respect of the last and is the reason for its omission in the present study. The reliability of the height span difference has been claimed by some authors (Pearson and Lee, 1902) but others have reservations unless it is used in conjunction with additional indices as in this study (Sinclair *et al.*, 1960). In this context, age is important, for both the height span difference and the ratio of the upper and lower body segments are less reliable during the growing period and after middle life when degrees of kyphoscoliosis tend to distort measurements. The importance of measuring several skeletal indices is well illustrated in this series, for of the 18 first degree relatives with skeletal abnormalities only 7 (38·9%) had more than one abnormal index.

The classical ocular abnormalities in Marfan's syndrome include a characteristic pattern of dislocation of the lens, which is typically small and globular (spherophakia) and may be associated with coloboma and localized nonprogressive dot opacities, iridodonesis, hypoplasia of the iris, poor dilatation of the pupils, secondary glaucoma from persistence of mesodermal elements in the draining angle of the anterior chamber, and various forms of peripheral degeneration and detachment of the retina (Duke-Elder, 1964).

In this study, 5 (9·8%) relatives had ocular defects which were thought to be directly related to Marfan's syndrome. This excluded 2 relatives with scattered dot opacities of the lens, a feature occasionally associated with the syndrome (Duke-Elder, 1964). A further 17 relatives had ocular defects which were considered unrelated, which included 7 with myopia, 5 with hypermetropia, and astigmatism, 3 with lenticular abnormalities (including the 2 with scattered dot opacities), 1 with optic disc abnormalities, and 1 with hypertensive retinopathy. Seven of these 17 (41·2%) relatives, however, had cardiovascular or skeletal abnormalities of the *formes frustes* of Marfan's syndrome, but these did not include the 2 relatives with scattered dot opacities of the lens. Once again this draws attention to the difficulty of interpreting isolated ocular abnormalities in the *formes frustes* of the disease.

GENETIC IMPLICATIONS AND CONCLUSIONS

Marfan's syndrome is a congenital disorder of connective tissue transmitted as an autosomal dominant. The fact that only 25 (37·3%) of the 67 living first degree relatives who were examined were affected rather than the expected 50 per cent may be the result of a number of factors, the most relevant probably being underdiagnosis of the less evident manifestations and the strict criteria used in this study. For example, if a metacarpal index of 8·0 rather than 8·4 had been accepted as it is by some authors, a further 6 relatives would have been included, and if the ocular abnormality of scattered lenticular dot opacities had also been considered compatible with Marfan's syndrome a further 2 would have been accepted bringing the total of affected first degree relatives to 33 (49·3%). Another factor accounting for the limited number of first degree relatives affected could be the early deaths of those with Marfan's syndrome, as our information about the 41 who had died was incomplete. Furthermore, the appearance of some clinical abnormalities in the cardiovascular system and eye are age related in spite of being genetically determined. In some of the younger first degree relatives, therefore, abnormalities may have been present but undetected. Finally, Bowers (1959) suggested that the fertility rate and ability to transmit the disease differed in the two sexes; affected males averaged only 1/11 as many children and 1/23 as many affected offspring as affected females. If this is correct, it may be relevant to the present study as 16 of the propositi were males and only 2 females.

There was nothing in our clinical data to suggest that the *formes frustes* had a different mode of inheritance from the classical syndrome. However, it is probable that we are looking at some of the pleiotropic effects of a single gene. Until the biochemical lesion has been determined, which may be in collagen or elastin biosynthesis, it is impossible to discuss the pleiotrophy in realistic terms as has been done for other collagen disorders such as the Ehlers-Danlos syndrome and osteogenesis imperfecta (McKusick, 1976).

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Experience with counterpulsation in cardiac surgical patients

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At Sheffield Regional Cardiothoracic Unit, the AVCO intra-aortic balloon pump has been used on 25 occasions in 21 months. Of the 25 patients, 12 survived and left hospital. The procedure is particularly beneficial in patients who have suffered some failure of myocardial protection during operation and to those who are suffering from acute ischaemia or the sequelae of myocardial infarction. The place of preoperative counterpulsation is discussed. Patients with long-standing cardiac disease who have emergency surgery benefit less from counterpulsation. Those patients with chronic ischaemic damage to the heart have nothing to gain from the use of counterpulsation.

The Sheffield Regional Cardiothoracic Unit obtained an AVCO intra-aortic balloon pump in 1974. Since that time, 25 patients have had the balloon inserted as a means of circulatory support and this group of patients is the subject of this report.

Patients and methods

The details of the 25 patients undergoing counterpulsation are set out in the Table.

INDICATIONS FOR SUPPORT BY COUNTERPULSATION

All patients who had cardiogenic shock which had failed to respond to the usual treatment were considered for the insertion of the intra-aortic balloon and treatment by counterpulsation. No distinction was made between patients with right and left ventricular failure. These patients were usually under surgical care but several were initially seen on medical wards. Cardiogenic shock was diagnosed when there was persistently low arterial blood pressure of below 80 mmHg systolic, urine output below 0·5 ml/kg body weight per hour, and persistently cold skin, associated with mean atrial pressures in the range of 20 to 30 mmHg. Cardiac output measurements were not made. In all patients, cardiogenic shock was initially treated for at least one hour usually by means of an intravenous infusion of adrenaline or noradrenaline. Persistent failure of the blood pressure to rise above 80 mmHg systolic and persistently low urine output and skin temperature led to the insertion of the intra-aortic balloon and treatment by counterpulsation.

TECHNIQUES OF INSERTION AND REMOVAL

In our experience the technique described by Kantrowitz *et al.* (1968) was reliable and applicable to all patients. The common femoral artery is exposed in the groin and a 12 mm Dacron graft is sewn onto the artery using 5/0 Prolene suture so as to form a prosthetic 'side arm' to the artery. The 30 ml balloon is then inserted into this side arm and advanced into the descending thoracic aorta. A thick suture tied around the tube graft then allows the balloon to lie in the arterial system without blood loss. This small operation usually takes about 25 to 30 minutes and may be performed under local anaesthesia. Removal of the balloon is easily performed and the side arm is then either trimmed and sutured or doubly ligated very close to the artery.

MONITORING OF PATIENTS RECEIVING COUNTERPULSATION

Most of our patients who required counterpulsation had had an open heart operation. Consequently these patients had a left atrial pressure line as well as a right atrial pressure line, arterial cannula, and urinary catheter. The usual indirect indices of cardiac output were measured but in no case was the cardiac output measured directly. In this group of very ill patients, it is easy to allow too many monitoring devices and cables to accumulate around the patient; we found that the pressures and electrocardiogram were best recorded on a

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single instrument and that the control of the counterpulsation pump was best achieved by a 'jump' lead from this monitor.

Results

Of the 25 patients who were subjected to counterpulsation, 12 left hospital alive (48%). Of those patients who died, 4 did so some time after showing an improvement with counterpulsation which persisted and allowed the balloon to be removed. Only 2 patients failed to show any improvement with counterpulsation.

Several groups, each requiring counterpulsation for a different reason, may be identified in this series of patients.

(1) PREOPERATIVE COUNTERPULSATION

(Cases 4, 17, 22, 25)

Four patients had the balloon inserted before operation. Two of these had an acute post-infarction ventricular septal defect (Cases 4 and 25) and were in very severe low output state; these patients subsequently underwent surgery successfully after counterpulsation for a period of 37 hours in one and 48 hours in the other. Another patient had a myocardial infarct with cardiogenic shock (Case 22) and responded well initially to counterpulsation. He died 48 hours later while being transferred for studies in the catheterisation room, and it is likely that the machine was not properly managed at the time of transfer. The remaining patient with severe multiple valve disease (Case 17) had the balloon inserted 18 hours before successful operation.

In each case there was an improvement in tissue perfusion which was often slow to start, occurring about 90 minutes after insertion of the balloon. Arterial blood pressure did not usually alter but skin temperature and urinary output rose and the patients' cerebration and metabolic state altered dramatically. When operation was undertaken, the patients were in a normal metabolic state and their morale was usually good.

In this subgroup, 3 of 4 patients survived and left hospital.

(2) EMERGENCY VALVE OPERATIONS

(Cases 2, 6, 7, 8, 9, 12, 21, 23)

Each of these patients came into hospital critically ill after a period of rapid deterioration at home or in

Table *Details of patients undergoing counterpulsation*

Case No.	*Age (y)*	*Sex*	*Nature of disease and operation*	*Duration of assistance*	*Outcome*	*Comments*
1	14	F	Routine repair tetralogy of Fallot	22 h	Death	RV failure ? divided coronary artery
2	35	F	Emergency MVR (clotted prosthesis)	12 h	Alive	Previous MVR, AVR, TVR; infected prosthesis
3	66	M	Ventricular aneurysm, post-infarction VSD; infarctectomy	60 h	Alive	Chronic lung disease; hypoxia
4	59	M	Post-infarction VSD	96 h	Alive	Preoperative support; required bilateral below-knee leg amputation
5	52	M	CABG + AVR	40 h	Alive	LVF postoperatively; proven infarct
6	38	M	Urgent AVR, TVR	100 h	Late death	Liver failure; previous MVR
7	50	M	Emergency MVR	19 h	Alive	RVF; previous open repair MV
8	63	M	Emergency MVR	72 h	Late death	Hepatic cirrhosis; long-standing disease
9	54	M	Emergency MVR	90 h	Death	Unable to wean
10	54	F	Routine AVR, MVR	2 d	Late death	Coronary atheroma prevented adequate perfusion of myocardium during operation
11	62	F	Routine MVR	3 d	Late death	Infarct before operation
12	38	M	Emergency AVR	40 h	Death	Previous prosthesis infected; large septal abscess; heart block
13	43	M	Emergency CABG × 2	1 d	Alive	Probably evolving myocardial infarction
14	51	M	Emergency CABG × 2	1 d	Alive	Evolving myocardial infarction
15	59	M	Routine AVR	24 h	Alive	Right coronary disease, arrhythmias
16	55	M	Routine AVR	20 h	Death	Diseased coronary arteries with abnormal distribution
17	48	F	Emergency AVR, MVR, TA	40 h	Alive	Preoperative assistance
18	52	M	CABG × 3	1 d	Alive	Incomplete endarterectomy LAD → infarct
19	57	M	CABG × 3	12 h	Alive	Possible myocardial infarct
20	60	M	Urgent LV aneurysmectomy	1 h	Death	Small aneurysm, extensive chronic damage to left ventricle
21	58	M	Emergency MVR	24 h	Death	Extensive visceral damage
22	50	M	Myocardial infarct, in shock	2 d	Death	No operation, technical problems with counterpulsation
23	51	M	Emergency AVR	18 h	Death	Disruption of previous prosthesis 24 hours before
24	48	F	Urgent LV aneurysmectomy	2 d	Death	Diffuse damage LV; new infarct
25	59	M	Post-infarction VSD	90 h	Alive	Preoperative support

MVR, mitral valve replacement; VSD, ventricular septal defect; CABG, coronary artery bypass graft; AVR, aortic valve replacement; TVR, tricuspid valve replacement; TA, tricuspid annuloplasty; RVF, right ventricular failure; LAD, left anterior descending coronary artery; LV, left ventricle; LVF, left ventricular failure.

another hospital. Most were semiconscious and uraemic on arrival and had persistently low blood pressures. Four patients in this group underwent emergency mitral valve replacement after many years of symptoms and deterioration; all 4 had been in hospital for some days before transfer to the unit; one patient had had haematemesis and another (Case 12) was jaundiced.

At operation, myocardial performance was not significantly improved after bypass in any of these patients. In all, the balloon was inserted during the operation after a period of one hour in which catecholamine infusion, correction of acidosis and arrhythmias had manifestly failed to improve cardiac function.

The average duration of counterpulsation after operation was 32 hours. Six patients were successfully weaned from support but 2 died subsequently. Two patients failed to support a circulation even with counterpulsation. Of the 4 patients undergoing emergency mitral valve replacement, only 2 survived to leave hospital.

(3) DAMAGE TO MYOCARDIUM DURING OPERATION (Cases 5, 10, 15, 16, 18, 19)

In each of these cases, operation was routinely performed, but during the procedure technical problems were encountered which rendered preservation of myocardial function difficult.

Case 5, who underwent aortic valve replacement, with coronary artery bypass grafting and endarterectomy, had an intraoperative myocardial infarct, presumably as a result of an inadequate endarterectomy. In Cases 10, 15, and 16, unexpected severe coronary arterial disease was encountered during aortic valve replacement rendering adequate coronary perfusion impossible. In each case, counterpulsation had to be started before the patient could be weaned from bypass. Our present policy of profound topical cardiac hypothermia results from this experience. Cases 18 and 19 were patients having multiple vein grafts applied for relief of angina. In Case 18, an endarterectomy had to be performed on the left anterior descending artery; a documented infarct and left ventricular failure probably resulted from incomplete endarterectomy. The other patient had a long and difficult operation to revascularise a poorly functioning ventricle, and it is probable that further myocardial damage occurred during the operation. In these 2 patients, counterpulsation was started 90 minutes and 300 minutes respectively after coming off bypass.

In this group, one death occurred during counterpulsation and one late death followed a satisfactory initial response.

(4) OPERATION FOR EVOLVING MYOCARDIAL INFARCTION (Cases 13 and 14)

Both of these patients underwent revascularisation surgery during an episode of prolonged severe chest pain associated with electrocardiographic abnormalities suggestive of an early infarct. In each case, when the chest was opened the cardiac output was very low and the left atrial pressure was high. After bypass, some improvement in ventricular function occurred but was inadequate to support a spontaneous circulation until the balloon was inserted. Both patients survived and left hospital.

(5) SALVAGE OPERATIONS FOR CHRONICALLY DAMAGED HEARTS (Cases 3, 20, 24)

Each of these patients was known to have a left ventricular aneurysm and had undergone acute deterioration a short time before operation. In each a large discrete ventricular aneurysm was found, but after resection, myocardial performance was inadequate to maintain a satisfactory circulation. Counterpulsation in two of the three cases was ineffective; these patients could not be weaned from bypass and died. At necropsy, diffuse chronic damage of the left ventricle was found.

(6) MISCELLANEOUS CASES

Case 1 had had a total repair of tetralogy of Fallot and had done well for 12 hours. Cardiac output then fell and remained low in spite of treatment. After 48 hours, when the patient was moribund, the balloon was inserted but counterpulsation produced only a temporary response.

Case 11, a patient of 62 years, underwent a routine mitral valve replacement. No technical difficulties or failure of myocardial preservation occurred. Cardiac output fell after operation and failed to respond to counterpulsation which was started 6 hours after operation and continued for 3 days. At necropsy there were signs of previous infarction of the left ventricle, which was thought to have occurred before operation.

Discussion

Intra-aortic balloon counterpulsation has been shown to increase the blood supply to ischaemic myocardium (Gill *et al.*, 1973) and also to reduce left ventricular work in the failing heart (Powell *et al.*, 1970). The clinical value of these haemodynamic changes has been shown by several groups of workers who have reported their results. The immediate response and short and long-term results of treatment with counterpulsation have been reported in patients who are shocked after myocardial infarction (Dunkman *et al.*, 1972; Scheidt *et al.*, 1973), and those who have poor cardiac function after operation (Buckley *et al.*, 1973). Counterpulsation has also been used in the management of patients with complications of myocardial infarction (Buckley *et al.*, 1973).

The group of patients reported here has been treated during a 21-month period at the Sheffield Cardiothoracic Unit. During this time approximately 500 open heart operations were performed in the Sheffield Hospitals. Counterpulsation has been used in 25 patients and certain types of patient may be identified who have most to gain from the support offered. Counterpulsation appears to be of value in patients who arrive in terminal stages of cardiac disease associated with profound metabolic disturbances and incipient organ failure. In our experience, patients suffering from the mechanical sequelae of myocardial infarction, such as an acute ventricular septal defect, do well as do some patients in the terminal stage of valvular heart disease. The conduct of the anaesthetic, perfusion, and operative procedure is simplified and provided that correction of the defect is achieved, the outlook is good. Similarly a good immediate response and late result were achieved in patients who sustained acute left ventricular myocardial damage during operation. Identical experience has been reported by Buckley *et al.* (1973).

The results of using counterpulsation were poor when chronic damage to the left ventricle had preceded operation and were very bad in those patients who had end-stage severe mitral valve disease, usually associated with chronic pulmonary vascular disease. Both of the patients who survived counterpulsation after emergency mitral valve operations were young and had had problems which, though severe, had been of short duration and which had begun in hospital.

One of these patients (Case 7) is of particular interest. This man of 50 years had had an open mitral valvotomy with freeing of fused chordae 10 days previously. Investigation after the development of sudden pulmonary oedema showed gross mitral regurgitation. At operation, there was necrosis of the tip of the anterior papillary muscle and both mitral leaflets were flail. Mitral valve replacement was performed and when bypass was discontinued, there was a very high pulmonary artery pressure and a high right atrial pressure together with a low left atrial pressure and inadequate cardiac output. The patient deteriorated further after operation and the counterpulsation was started in a desperate attempt to save his life. Improvement was dramatic and may have been the result of improved oxygen delivery to a failing high pressure right ventricle. The phasic flow pattern of the coronary arterial supply to the normal right ventricle has been shown to be mainly systolic in timing, whereas that to the normally functioning left ventricle is mostly diastolic (Fixler *et al.*, 1973). Presumably a high pressure right ventricle has a supply similar to that of the left ventricle and the effect of counterpulsation in this instance was to improve the diastolic coronary blood flow to the right ventricle. Case 1, a patient with right ventricular failure after total repair of tetralogy of Fallot, might have improved also had counterpulsation been started earlier.

Some authors have stated that counterpulsation was not a useful procedure (Effler, 1975) and was unnecessary in surgical practice. While certain of the indications for counterpulsation are avoidable, especially by adequate myocardial protection during operation, there remains a group of patients which presents to the cardiologist or surgeon with acute but reversible damage to the myocardium. Surgical correction cannot always result in sufficient immediate improvement in function to maintain an adequate circulation without assistance. The use of counterpulsation in this group of patients has had encouraging results and has undoubtedly saved patients who would otherwise have died.

We have found that the AVCO intra-aortic balloon pump is a most reliable instrument and is easy to use and to understand. The nursing staff, in particular, have felt happy to manage patients who have been treated with it.

We thank Mr. D. G. Taylor for permission to report Cases 1 and 23 who were admitted to hospital under his care.

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Chronic bilateral bundle-branch block

Long-term observations in ambulatory patients

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During a period of 28 months, all patients (79) who presented with bilateral bundle-branch block were selected for study from a private practice outpatient population. They were followed prospectively from the date of entry into the study and their charts were reviewed retrospectively. The average age of the participants was 73·3 years and they were observed clinically for a cumulative period of 4237 months (353·08 years).

A high incidence of severe heart disease and death was noted among the study group. Twenty-four (30·3%) had a New York Heart Association functional classification of 3 or 4. Eight (10·1%) died. Only one patient died suddenly and he had had a stable electrocardiographic pattern of bilateral bundle-branch block for a period of 118 months (9 years 10 months). Seven patients required permanent pacemakers. In 6 instances death resulted from pump failure; in one it was the result of lung cancer. In none of these 7 individuals did rhythm disturbances contribute to death. In most cases vertigo was not of cardiac origin (88·2%). Eight patients had 11 major surgical procedures with no significant cardiac sequelae.

Our observations suggest that elderly patients with chronic bilateral bundle-branch block should be managed conservatively. The prognosis in these patients appears primarily to be related to the degree of myocardial disease rather than to the conduction disorder.

In 1968 interest was rekindled in the clinical course of patients manifesting one of the electrocardiographic patterns of bilateral bundle-branch block (Lasser, Haft, and Friedberg, 1968), left axis deviation, and right bundle-branch block. These investigators reviewed 5500 consecutive hospital charts and found a 1 per cent (55 patients) incidence of the pattern of left axis deviation and right bundle-branch block. Of these 55 patients, 9 per cent (5) had third degree atrioventricular block.

Bilateral bundle-branch block is a commonly observed conduction disturbance especially in the elderly, and the electrocardiographic patterns associated with it have been well established (Rosenbaum and Lepeschkin, 1955; Lenegre, 1964; Lepeschkin, 1964; Schloff *et al.*, 1967; Langendorf and Pick, 1968; Rosenbaum, 1968; Watt and Pruitt, 1969; Rosenbaum *et al.*, 1969; Rosenbaum, 1970; Scanlon *et al.*, 1970; New York Heart Association Criteria Committee, 1973). Electrophysiological studies (His bundle recordings) have confirmed the most common site of atrioventricular block to be in the proximal His-Purkinje system (infranodal) (Damato *et al.*, 1969; Schuilenburg and Durrer, 1970; Rosen *et al.*, 1972; Spurrell *et al.*, 1972; Kunstad *et al.*, 1973). In spite of the recently acquired electrophysiological knowledge of atrioventricular block and usual easy recognition of the electrocardiographic manifestation of bilateral bundle-branch block, the appropriate clinical approach to this large group of patients has not yet been fully clarified. The report presented here is based upon clinical observations of 79 subjects with chronic bilateral bundle-branch block who were selected from a fully ambulatory outpatient population. Its purpose is to help define the prognosis for this patient group and thus aid in arriving at a rational approach to their medical management.

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Patient selection and clinical observations

The subjects for this study were selected from the authors' respective practices. All patients who had the electrocardiographic manifestations of bilateral bundle-branch block as defined by the Criteria Committee of the New York Heart Association and who presented in the office for examination between 1 September 1972 and 31 December 1974 were included in the investigation. Each participant was examined, and if his chart originated in our offices it was reviewed retrospectively; previous records from other physicians were excluded. Therefore, in many cases the electrocardiographic patterns of bilateral bundle-branch block may have been present for a significantly longer period of time than has been tabulated. During the entire period of clinical observation each patient was followed by a single physician.

The mean age of our patient population, which consisted of 50 men and 29 women was 73·3 years with a range from 48 to 87 years. The cumulative period of clinical observation amounted to 4237 months (353·08 years), the shortest period of observation was 1 month and the longest 195 months, with a median period of 38 months and a mean of 53·6 months.

A wide spectrum of heart diseases was encountered, the diagnoses being based on accepted clinical criteria and/or the result of cardiac catheterisation. The majority, 68·3 per cent (54 patients), had ischaemic heart disease and 17·7 per cent (14 patients) had hypertension. In the hypertensive group, 6 also had ischaemic heart disease. Cardiomyopathy with normal coronary arteries and impaired ventricular function was detected by cardiac catheterisation in 6·3 per cent (5 patients). Rheumatic heart disease was diagnosed in four patients; three of these also had ischaemic heart disease. Two patients had pulmonary heart disease, one had scleroderma, and in 8·9 per cent (7 patients) the heart disease was of uncertain aetiology.

The New York Heart Association Functional Classification is listed in Table 1 for the 79 patients. Angina was found to be by far the most common symptom, occurring in 67·1 per cent (53 patients). Exertional dyspnoea was noted by 43 per cent (34 patients), palpitation by 24·1 per cent (19 patients), vertigo in 21·5 per cent (17 patients), and syncope in 5·1 per cent (4 patients).

Table 2 contains the frequency of the different electrocardiographic patterns encountered in our series in association with bilateral bundle-branch block. The majority, 83·5 per cent (66 patients), had left axis deviation and right bundle-branch block. The other patterns observed were right axis deviation and right bundle-branch block, and left bundle-branch block superimposed upon right bundle-branch block. Eleven subjects had Q waves suggestive of transmural myocardial infarction; 12 had first degree atrioventricular block; and 6 had chronic atrial fibrillation.

Table 1 *New York Heart Association functional classification at end of observation period*

Class	*No. of patients*	*Percentage*
1	13	16·5
2	42	53·2
3	16	20·2
4	8	10·1
Total	79	100·0

During the 28 months of this investigation, 7 of our patients required permanent pacemakers. Only 4 of these pacemakers were necessitated by atrioventricular block; 2 were required because of sinoatrial dysfunction; and 1 had to be implanted for acute advanced atrioventricular block 20 days after a myocardial infarction. This latter patient died in the hospital 48 hours after the implantation and at necropsy the pacemaker was tested and found to be functioning properly. Three of the four patients who required pacing because of progression of their bilateral bundle-branch block to a higher degree of atrioventricular block presented with syncope and complete atrioventricular block.

Within the period of active observation, 4·5 per cent of the patients with left axis deviation and right bundle-branch block and 8·33 per cent of those with right axis deviation and right bundle-branch block required pacemaker implantation because of the development of second or higher degree atrioventricular block. Though most of the subjects were in

Table 2 *Electrocardiographic observations and associated requirements for pacemaker implantation*

ECG pattern	*No. of patients*	*%*	*Patients requiring pacemakers*			
			No. of patients	*%*	*Observation (mth) before implant*	*PR (s)*
LAD+RBBB	66	83·5	3	4·5	34, 79, 202	0·2 (2 had AF)
RAD+RBBB	12	15·2	1	8·3	15	0·2
LBBB superimposed on RBBB*	1	1·3				
Q waves suggestive of transmural infarction	11	13·9				
1° AV block (PR >0·20 s)	12	15·2	1	8·3		
Chronic atrial fibrillation	6	7·6	2	33·3		

*HV interval prolonged 70 ms

sinus rhythm and had normal PR intervals, of the 4 patients who developed second or higher degree atrioventricular block, 2 had chronic atrial fibrillation and 1 had a prolonged PR interval; only 1 had sinus rhythm with a normal PR interval (Table 2).

Vertigo was a relatively common symptom, occurring in 17 patients (11·8%). In only 2 patients, however, was it of cardiac origin. In contradistinction, of the 4 patients with syncope, 3 (75%) were caused by the conduction defect and usually indicated the onset of a higher degree of atrioventricular block.

Eight patients (10·1%) died during the study period. One of these individuals expired suddenly and represented the only case in which death might conceivably have been ascribed to the sudden onset of atrioventricular block or a rhythm disorder. This sudden death occurred in an asymptomatic 76-year-old man who was known to have had bilateral bundle-branch block for at least 118 months (9 years and 10 months). Six of the other patients who died were functional class 4 and death was the result of their heart disease. These latter patients did not develop any significant rhythm disturbances. One patient died of lung cancer. Table 3 presents the significant data pertaining to the 8 deaths.

Eight of our study participants had 11 major surgical procedures under general anaesthesia. Of these, one patient underwent in separate operations a triple coronary bypass, resection of an aortic aneurysm, and a cholecystectomy. Another patient had a double coronary bypass. One patient each had subtotal gastrectomy for carcinoma, cholecystectomy, suprapubic prostatectomy, hip pinning, and laparotomy. In no instance did a significant rhythm disturbance complicate the intra- or postoperative course.

Discussion

South Florida has a large geriatric population among whom intraventricular conduction defects are exceedingly common (Burch, 1975). Thus, we had no difficulty in selecting 79 elderly patients with bilateral bundle-branch block for clinical observation.

Our study confirms two especially important findings previously recorded by others: (1) bilateral bundle-branch block is associated with a high incidence of severe heart disease; and (2) it is uncommon for bilateral bundle-branch block to progress to second or higher degree atrioventricular block (De Pasquale and Bruno, 1973; Dhingra *et al.*, 1974, 1975; Denes *et al.*, 1975). In our series 30·3 per cent (24 subjects) had functional class 3 and 4 heart disease and in 5·1 per cent of cases (4 subjects) second or higher degree atrioventricular block developed.

As noted previously, 8 of our patients died during the 28 months of the study. Of the 8, 6 were classified as functional class 4. Five of the latter died as a result of pump failure without significant associated arrhythmias; the other died in the hospital after a myocardial infarction with a recently implanted properly functioning pacemaker. Lastly, as mentioned above, one patient died of lung cancer and there was one sudden unaccountable death. This was the only subject in our group who might have died from a progression of his bilateral bundle-branch block to higher degree atrioventricular block.

Although seven (8·8%) subjects required pacemakers, only 4 (5·1%) needed pacing because of progression of their atrioventricular conduction disturbance. Of these 4, 3 presented with syncope and slow idioventricular rhythm and one with vertigo and second degree atrioventricular block. In all 4 it was not clinically deleterious that second or higher degree atrioventricular block rather than bilateral bundle-branch block with 1:1 atrioventricular conduction was used as the indication for pacemaker implantation. In all of these subjects the course after pacemaker implantation was uncomplicated.

As expected, in the presence of infranodal atrioventricular conduction defects there was an associated high incidence of supraventricular conduction disturbances (Lev *et al.*, 1974). Twelve (15·2%) subjects had prolonged PR intervals and 6

Table 3 *Patient deaths*

Cause of death	*No. of patients*	*NY Heart Assoc. Class*	*Period of observation before death (mth)*	*Pacemaker*
Sudden, unknown	1	1	118	No
Pump failure	5	4	57, 70, 83, 85, and 131	No
Sudden, in hospital 48 hrs after pacer implant*	1	4	103	Yes
Ca lung	1	2	120	No

*Twenty-two days after acute myocardial infarction.

(7·8%) had chronic atrial fibrillation. It is of interest that of the 4 patients who experienced progression of their infranodal atrioventricular conduction disturbance to a higher degree of atrioventricular block, 2 had chronic atrial fibrillation, 1 had a prolonged PR interval, and 1 had sinus rhythm with a normal PR interval. This suggests that chronic atrial fibrillation in association with bilateral bundle-branch block may be a poor prognostic sign.

This study again confirms that prophylactic pacing is not indicated (Berg and Kotler, 1971) in patients with bilateral bundle-branch block who have to undergo general anaesthesia. Again, as noted above, 8 of our patients were subjected to 11 major surgical procedures without mishap.

Although vertigo and syncope are considered accompaniments of higher degree atrioventricular block, in the elderly they may frequently be the result of non-cardiac disorders (De Pasquale and Bruno, 1973, 1974; Dhingra *et al.*, 1974; Burch, 1975; Denes *et al.*, 1975). In our series only 2 of 17 cases of vertigo were attributable to rhythm disturbances; however, 3 of 4 syncopal episodes were the result of atrioventricular block. In a recent report by Dhingra *et al.* (1974) who also studied patients with chronic bilateral bundle-branch block, most episodes of syncope were not the result of the cardiac disorder. These investigators further noted that in their population of 130 patients syncope did not portend a grave prognosis. Our data tend to confirm this observation but in our group syncope did not occur frequently enough to draw conclusions regarding its prognosis.

His bundle electrography has added a great deal to our knowledge of atrioventricular conduction disturbances. Narula *et al.* (1975) reported data that strongly suggested the incidence of death per year is five times higher in patients with prolonged HV times than in those with normal HV times when the surface electrocardiograms showed the pattern of right bundle-branck block and left anterior hemiblock. They recommended that asymptomatic patients with right bundle-branch block and left anterior hemiblock whose HV times were 70 ms or longer should be considered for permanent pacemaker implantation. Their same study, however, implicated the severity of the heart disease as a main determinant for death when they found that of the 29 patients with prolonged HV intervals who died during the follow-up period 10 had permanent pacemakers. Of the other 19 who did not have pacemakers, 9 died of causes unrelated to atrioventricular block.

In a His bundle electrogram study of 50 patients with bilateral bundle-branch block exhibiting Mobitz II block or transient complete atrioventricular block, Vera *et al.* (1976) recommended that pacemakers be implanted in patients whose HV intervals were 65 ms or longer. Because that was a retrospective series His bundle recordings were undertaken only in the group of patients who had already exhibited high degrees of infranodal atrioventricular block. Dhingra *et al.* (1975) studied 21 patients with long-term right bundle-branch block and left posterior hemiblock and concluded that this pattern was associated with less trifascicular disease than previously reported and that the clinical course of most patients was benign. Wu *et al.* (1976) reported in a study of alternating bundle-branch block that the clinical course was primarily determined by the severity of the heart disease and not by the occurrence of atrioventricular block.

Other reports of His bundle studies in patients with bilateral bundle-branch block have shown that in most cases the results of these studies are not clinically useful in determining which patients with infranodal atrioventricular conduction defects are in danger of progressing to higher degrees of atrioventricular block (De Pasquale and Bruno, 1974; Dhingra *et al.*, 1974; Denes *et al.*, 1975; Rosen *et al.*, 1975). With some exceptions bilateral bundle-branch block is clearly shown by the electrocardiogram (Langendorf, Cohen, and Gozo, 1972), and it appears that for the most part individual prognoses are determined by the severity of the myocardial disease rather than by the conduction disorder (De Pasquale and Bruno, 1973, 1974; Dhingra *et al.*, 1974; Denes *et al.*, 1975; Burch, 1975).

Clinical implications

Infranodal atrioventricular conduction disorders are not uncommon among senior citizens (Burch, 1975). Our data, together with the findings of others, indicate that the rational medical approach to the problem should be conservative (Burch, 1975; De Pasquale and Bruno, 1973, 1974; Dhingra *et al.*, 1974; Denes *et al.*, 1975; Lev *et al.*, 1974; Rosen *et al.*, 1975). What continues to be needed is appropriate clinical observation including some form of continuous electrocardiographic monitoring when symptoms indicate, as well as prompt therapeutic intervention when second or higher degree atrioventricular block is observed.

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The normal electrocardiogram as a predictor of left ventricular function in patients with coronary artery disease

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Fifty-five consecutive patients with a normal resting electrocardiogram and coronary artery disease were examined to determine left ventricular function. Fifty-two (95%) had no evidence of left ventricular asynergy; 3 patients had only mild hypokinesis. Of this group of patients, 25 (47%) had one vessel disease, 17 (30%) had two vessel disease, and 13 (23%) had three vessel disease.

Significant left ventricular asynergy was not not found in patients with coronary artery disease and normal electrocardiograms. In addition, a normal electrocardiogram was not related to the number of coronary arteries involved.

Left ventricular function is one of the important factors in the prognosis of patients with coronary artery disease. Patients with normal haemodynamic states and normal ventriculograms have a far better prognosis than those with abnormal haemodynamic states and abnormal ventriculograms (Bruschke *et al.*, 1973; Burggraf and Parker, 1975). The assessment of left ventricular function is often made from non-invasive methods such as the chest *x*-ray, electrocardiogram, vectorcardiogram, systolic time intervals (Weissler *et al.*, 1972), echocardiogram (Jacobs *et al.*, 1973), and B-ultrasonography of the heart (Teichholz *et al.*, 1973).

The value of pathological Q waves in the electrocardiogram as predictors of the presence, site, and severity of left ventricular asynergy in the majority of patients is accepted by most investigators (Proudfit *et al.*, 1966; Bordia *et al.*, 1970; Welch *et al.*, 1970; Hilsenrath *et al.*, 1972; Williams *et al.*, 1973; Miller *et al.*, 1974; Bodenheimer *et al.*, 1975). Furthermore, the presence of Q waves makes reversibility of left ventricular asynergy unlikely by nitroglycerin administration (Helfant *et al.*, 1974; Banka *et al.*, 1974) or by myocardial revascularization (Chatterjee *et al.*, 1973).

However, the value of a normal electrocardiogram in predicting normal left ventricular function in patients with coronary artery disease particularly has not been evaluated. Because of its pronounced clinical and epidemiological significance, a study was designed to test its validity.

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Subjects and methods

A consecutive retrospective review of patients with angiographically documented coronary artery disease and normal resting electrocardiograms was made in 55 subjects. A normal resting 12 lead electrocardiogram was defined by the conventional criteria (Simonson, 1961), in the absence of pathological Q waves, hypertrophy patterns, conduction abnormalities or abnormalities of repolarisation (e.g. non-specific ST-T wave changes). The electrocardiograms were analysed by three different cardiologists and accepted only if they were considered normal by all observers. Patients with valvular heart disease and cardiomyopathies were excluded.

Selective left and right coronary angiography was accomplished by the Sones or Judkins technique. Coronary artery disease was defined as the presence of one, two, or three coronary arteries with at least 70 per cent obstruction of their lumen.

Left ventricular end-diastolic pressure was recorded in the resting state. Left ventriculography was performed with the patient in a 30° right anterior oblique projection. A frame-by-frame motion analysis (Herman *et al.*, 1967) was carried out, and the ventricle was divided into inferior, apical, and anterior segments. The size, shape, and

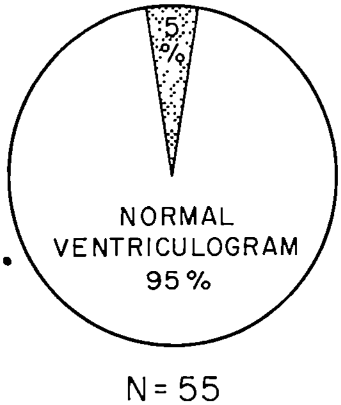

Fig. 1 *Left ventricular function in patients with coronary artery disease and normal electrocardiogram. n = number of patients.*

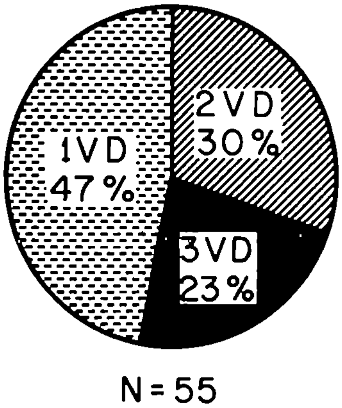

Fig. 2 *Severity of coronary artery disease in patients with normal electrocardiograms. n = number of patients.*

contractility pattern was noted, and the presence or absence of asynergy was identified. Ejection fractions were calculated from the Dodge formula (Sandler and Dodge, 1968).

Results

Fifty-five consecutive patients with normal electrocardiograms and angiographically-proved coronary artery disease constitute the group of this analysis. There were 52 men, and 3 women with a mean age of 49 years (range: 34 to 63). Of this group of patients, all were symptomatic of angina pectoris for periods of 6 months to 12 years. Twenty-nine were classified by cardiac status in class II by the criteria of the New York Heart Association, 20 in class III, and 6 in class IV.

Fifty-two patients (95%) with normal resting electrocardiograms and significant coronary artery disease had no evidence of left ventricular asynergy and their ventriculogram was considered normal (Fig. 1). One patient had mild hypokinesis involving the apical segment, and 2 patients had mild hypokinesis of the inferior aspect of the left ventricle. No patient had severe hypokinesis, akinesis, or dyskinesis.

The ejection fractions were normal for the entire group. Left ventricular end-diastolic pressure was above 12 mmHg in 12 of 55 patients. It was normal in the 3 patients with mild asynergy.

In this group of patients with coronary artery disease and normal electrocardiograms, 25 (47%) had single vessel disease and 17 (30%) had double vessel disease (Fig. 2). Though 47 per cent had single vessel disease, 53 per cent had significant double and triple vessel disease in the presence of a normal electrocardiogram. Of the 3 patients with mild hypokinesis, 2 had triple vessel disease and 1 had double vessel disease.

Discussion

Our data indicate that a normal electrocardiogram in the evaluation of the patient with angina pectoris predicts with a high degree of reliability normal left ventricular contractility without asynergic segments. Significant left ventricular asynergy was not found in this group of 55 patients. Ninety-five per cent of these patients had normal ventricular contraction, while 5 per cent showed only mild hypokinesis. At the same time, a normal electrocardiogram had no correlation with the presence or degree of coronary artery disease present. Other investigators (Likoff *et al.*, 1975; Bjork *et al.*, 1967; Martinez-Rios *et al.*, 1970) have clearly shown that significant coronary artery disease may exist in the presence of a normal resting electrocardiogram. Even patients with significant left main coronary artery stenosis may have a normal resting electrocardiogram (Cohen *et al.*, 1972). The absence of electrocardiographic signs of ischaemia could be related to the presence of adequate blood supply to the affected myocardium at rest (Martinez-Rios, *et al.*, 1970) or to inadequate sensitivity of the standard electrocardiogram to detect early stages of myocardial ischaemia.

Recently, other groups (Hilsenrath *et al.*, 1975, Gottlieb *et al.*, 1975) have evaluated the relation of left ventricular contraction pattern in patients with coronary artery disease with the electrocardiogram and vectorcardiogram. Of 230 patients (Hilsenrath *et al.*, 1975), 53 had normal electrocardiograms and vectorcardiograms. Of these, 38 (72%) had normal left ventricular contraction. Nine patients (17%) had anteroapical asynergy and 4 (7%) had isolated inferoposterior asynergy. In 2 patients, both inferoposterior as well as anteroapical asynergy was shown. In another study (Gottlieb *et al.*, 1975), 71 to 78 per cent of patients with equal or greater than 75 per cent coronary occlusion and normal electrocardiograms had normal ventriculograms. The difference between these studies and ours can be attributed to the difference in the definition of a normal electrocardiogram. Our study excluded all those with ST-T wave changes, among which asynergy is a prevalent finding.

It is of note that a raised left ventricular end diastolic pressure was noted in 12 of the 55 patients having normal electrocardiograms and normal ventriculograms. This finding may best be explained by a decrease in the left ventricular diastolic compliance in these patients with coronary artery disease which may occur earlier in some patients than the wall motion abnormalities.

The presence of a normal electrocardiogram, and its correlation with a normal left ventriculogram is of special relevance in the clinical evaluation of the patient with coronary artery disease. Medical therapy of angina in these patients is associated with a better prognosis as compared with those patients with abnormal left ventriculogram (Bruschke, *et al.*, 1973; Burggraf and Parker, 1975). This prognosis will depend mainly on the number of coronary arteries involved (Friesinger *et al.*, 1970; Bruschke *et al.*, 1973). Furthermore, if revascularization surgery proves to be effective in the preservation of jeopardized myocardium, this objective will be best accomplished in the patient with a normal left ventricle.

In conclusion, a normal electrocardiogram in patients with coronary artery disease is a most valuable predictor of a normal left ventricle just as an abnormal electrocardiogram is a reliable predictor of left ventricular asynergy.

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International Society of Cardiology

The Council on Epidemiology and Prevention of the International Society of Cardiology announces its 10th Ten Day International Teaching Seminar on Cardiovascular Epidemiology and Prevention, to be held in Ghana, 21 August to 2 September, 1977. Approximately 30 Fellows can be accepted. Final selection will be made by the Council's Seminar Committee. Nominees should be at the post-doctoral level, with some residency training or its equivalent, and be interested in cardiovascular epidemiology. Except in unusual circumstances, preference will be given to younger candidates, with little or no formal training in epidemiology. Limited funds may be available to give partial assistance with travel costs for accepted Fellows. Room and board are provided, without cost, to Fellows. *Fluency in English is essential.*

Three documents are required for application and should be sent at time of application: A letter of nomination submitted by chief of department or institution, a personal letter of application from the nominee, and the applicant's curriculum vitae. These should be received before the deadline for application, 1 May, 1977.

They should be sent to:

Jeremiah Stamler, M.D., Chairman,
Council on Epidemiology and Prevention, ISC,
Northwestern University Medical School,
Ward Building—Room 9–105
303 East Chicago Avenue,
Chicago, Illinois 60611, U.S.A.

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Clinical value of quantitative analysis of ST slope during exercise

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The diagnostic performance of automatic analysis of the exercise electrocardiogram in detecting ischaemic heart disease was studied in 147 patients with angiographically documented coronary disease. The results were compared with the results of visual analysis of the same recordings. Using a bicycle ergometer we tried to reach at least 90 per cent of the predicted maximal heart rate of the patient. Two bipolar thoracic leads (CM5, CC5) were used. In the visual analysis the criterion of the so-called ischaemic ST segment was applied. For the automatic analysis the population was divided into a learning group (N=87) and a testing group (N=60). In the learning group first critical values were computed for different ST measurements that provided optimal separation between patients with (CAG. POS.) and without (CAG. NEG.) significant coronary stenoses as revealed by coronary arteriography. These critical values were kept unchanged when applied to the testing group. With respect to the visual method an increase of the sensitivity by 0·45 and 0·36 was obtained by the automatic analysis in the learning and testing group, respectively. The best separation between CAG. POS. and CAG. NEG. group was reached using a criterion consisting of a linear combination of the slope of the initial part of the ST segment and the ST depression; the sensitivity being 0·70 and 0·60, respectively, in the learning and testing group. Using a criterion based on the area between the baseline and the ST segment (the SX integral) these values were 0·42 and 0·49, respectively. All specificities were kept to at least 0·90.

Exercise electrocardiography plays an important role in the detection and assessment of ischaemic heart disease. It is a simple method for identifying coronary insufficiency especially in those patients in whom the history is atypical (Bartel *et al.*, 1974). Furthermore because of its reproducibility, the test is frequently applied in the assessment of therapeutic and surgical treatment; the test also appears to have prognostic value (Ellestad and Wan, 1975). However, even if submaximal to maximal stress testing is used, some subjects fail to show electrocardiographic changes though their coronary arteriograms show significant stenoses (Ascoop *et al.*, 1971). Various investigators studied new criteria which were introduced to increase the detection rate in patients with coronary disease. At the same time, however, the number of false positive cases rises because of observer variance (Punsar *et al.*, 1968; McConahay *et al.*, 1970). Measurements are performed more consistently by computer analysis (Sheffield *et al.*, 1969; Ascopp *et al.*, 1974; Yanowitz *et al.*, 1974). It was the purpose of this study to assess various new criteria in exercise electrocardiography. Optimal critical values for these criteria were first derived in a 'learning population'; subsequently the diagnostic value of the criteria thus defined has been verified in a 'testing population'.

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The QRS-T wave analysis was performed with the help of a digital computer; the exercise-induced electrocardiographic changes in each patient were compared with the findings from coronary angiography (CAG).

Subjects and methods

(1) One hundred and forty-seven consecutive patients, all men suspected of having ischaemic heart disease, were studied. The learning population consisted of 87 patients with an average age of 46 (±7) years; the testing population comprised 60 patients with an average age of 50 (±8) years. Previous examination in other hospitals from which the patients were referred yielded negative exercise electrocardiograms by visual analysis in most of them.

The conditions for inclusion in this study were: (a) Normal repolarisation in the resting electrocardiogram; (b) no other cardiac disease present, except that which could be considered the result of ischaemic heart disease; (c) digitalis, beta-blocker, and antiarrhythmic agents were withheld two weeks before testing.

There were 6 patients in the learning group and 8 patients in the testing group with an infarct pattern.

(2) A graded exercise test was performed in all patients imposing a multistage increasing workload by means of a calibrated bicycle ergometer. Starting at an external load of 60 Watt the load was increased every 3 minutes by 30 W until a target heart rate was reached of 90 per cent of the maximum heart rate predicted for the patient (Sheffield and Reeves, 1965), or until one of the 'stop' criteria was met (Ascoop *et al.*, 1971).

(3) Recordings were made before the test (sitting), at the end of each exercise stage, and during the first 5 minutes of the recovery phase. The recorder is of the ink-jet type, frequency response linear up to 900 Hz, and with a time constant of 0·01 s; the paper speed was 25 mm/s. At the same time the signal was stored on magnetic tape using an FM recorder (Philips Analog 7, 9·5 cm/s).

(4) The electrocardiographic signals were derived from 2 bipolar thoracic leads with a common positive electrode at the position V5 of the standard electrocardiogram and the negative electrodes at the manubrium sterni (lead CM5) and at the position of V5R (lead CC5) (Blackburn *et al.*, 1967).

(5) In the visual interpretation of the graphical recordings the standard criterion of ischaemic ST segment was applied and defined as follows: (a) a junction depression of at least 100 microvolts with respect to the 'QQ' baseline; (b) followed by a horizontal or downsloping ST segment of at least 80 ms duration. A test was considered positive if 3 successive complexes showed an ischaemic ST segment at the stage of maximal load or during the first 3 minutes of the recovery phase, provided that the repolarisation wave at rest (sitting) was normal (Ascoop *et al.*, 1971).

(6) Computer analysis was performed only on electrocardiograms made at the stage of maximal exercise load; these recordings comprise 30 seconds, about 20 seconds of which are averaged coherently after removal of aberrant complexes. By this method a single averaged complex is obtained; onset and end of its QRS wave are determined using a template method (Van Bemmel *et al.*, 1973).

The baseline is defined at the level of the mean amplitude of the 10 ms sampling interval just before the QRS complex (sampling rate 300 Hz). ST depressions, ST slopes, both up- and downgoing and SX integrals are then computed, to establish new criteria.

ST DEPRESSIONS

These ST depressions measured at 1, 10, and 50 ms after the end of the QRS are called D0, D10 and D50, respectively.

ST SLOPES (SL)

These were calculated extending over three different intervals after the QRS complex: from 0 to 80 ms (SL 0–80), from 10 to 50 ms (SL 10–50), and from 50 to 70 ms (SL 50–70); (Fig. 1 C, D, E).

SX INTEGRAL

This was computed as the surface area between baseline and the negative part of the ST segment from junction to point X, the first intersection between baseline and ST segment, but in no case further than the end point of the ST segment (Fig. 1A and B).

In addition the diagnotsic value of both ST depression and ST slope in combination are analysed: D0 with SL 0–80: (D0, SL 0–80) D10 with SL 10–50 (D10, SL 10–50) and D50 with SL 50–70 (D50, SL 50–70) (Fig. 1 C, D, E).

(7) The criteria described above were considered to predict the degree of coronary stenoses. The severity of coronary disease was determined independently by selective coronary arteriography according to Sones' technique, with additional craniocaudal projections (Sones and Shirey, 1962; Ludwig and Bruschke, 1973).

The published work (Bartel *et al.*, 1974) and our own experience (Van Herpen *et al.*, 1970) indicates that stenoses of at least 70 per cent of the lumen diameter in a major coronary branch are haemodynamically significant; the coronary arteriogram showing such lesions was classified as positive (CAG. POS.).

All other angiograms were classified negative (CAG. NEG.). The relation between prediction (exercise electrocardiogram) and reality (CAG) is presented in a yes-no association matrix. The number of correctly predicted CAG. POS. cases divided by the total number of positive cases is called the sensitivity of the test (correct positive fraction); the number of correctly predicted CAG. NEG. cases divided by the total number of CAG. NEG. cases is the specificity of the test (correct negative fraction). Critical values for the abovementioned criteria of ST depressions, ST slopes, and SX integral were determined in such a way that optimal separation between the CAG. POS. and the CAG. NEG. group was achieved in the learning population.

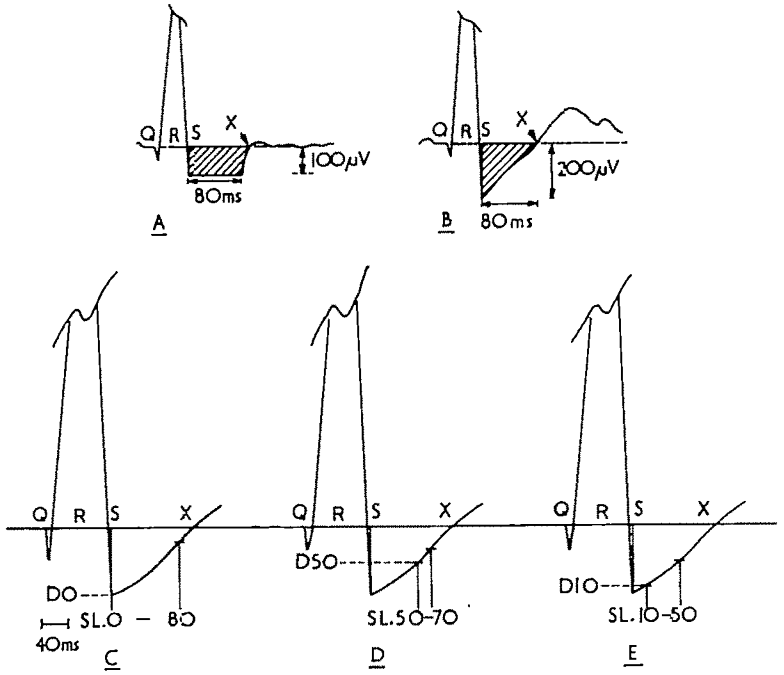

Fig. 1 *Different measuring points on the QRS-T complex for calculating SX integral (A and B), ST depressions, and slopes (C, D and E).*

We considered the separation optimal when a maximal sensitivity was achieved at a specificity of at least 0·9. These critical values of the criteria were subsequently kept unchanged when applied to the testing population.

Results

(1) CORONARY ARTERIOGRAM

Among the 87 patients of the learning population, 57 patients belonged to the CAG. POS. group (stenoses of at least 70 per cent in a major coronary branch). Of these 57 patients, 35 had an occlusion of at least one major branch. In this population 30 patients belonged to the CAG. NEG. group (stenoses of less than 70 per cent) and 26 of them had no coronary sclerosis at all.

In the testing population of 60 individuals, 39 patients were found to have significant coronary disease (CAG. POS.); 22 of them had an occlusion in at least one major coronary artery. Twenty-one patients belong to the CAG. NEG. group and in 13 of them no coronary sclerosis was detected.

(2) VISUAL ANALYSIS OF EXERCISE ELECTROCARDIOGRAM

Of the patients in the learning population, 14 showed ischaemic ST depressions, and all were CAG. POS. The same analysis in the test group resulted in 11 positive responses, all in CAG. POS. cases. There was thus a specificity of 1·00, but the sensitivity of this visual analysis in the learning and testing group was only 0·25 and 0·28, respectively. Seventy per cent of the patients who showed a positive test were detected using lead CM5 only.

(3) COMPUTER ANALYSIS OF EXERCISE ELECTROCARDIOGRAM

ST depressions

In the learning population the best results were obtained if the depression was measured 50 ms after the end of the QRS complex (D50) using a critical value of 35 microvolts in lead CC5 (Table 1). Sensitivities of 0·56 and 0·44 were then attained using leads CC5 and CM5, respectively. In the test population the sensitivity turned out to be 0·67 and 0·49 using leads CC5 and CM5, respectively (Table 2).

ST slope

In the learning population the best predictions were obtained by the analysis of the slope of the early part of the ST segment (SL 10–50). The critical value for the SL 10–50 in lead CC5 is 180 microvolts per 100 ms and for SL 0–80 220 microvolts per 100 ms. Sensitivities of 0·65 and 0·54 were found for leads CC5 and CM5, respectively. Practically identical

Table 1 *Results in learning population (N=87) : 57 patients with significant coronary disease (CAG. POS.) ; 30 patients without significant coronary disease (CAG. NEG.)*

Lead	*Criterion*	*Critical values*	*Sensitivity*	*Specificity*
CC5	D 10	D >154	19/57=0·33	27/30=0·90
	SL 10–50	SL ≤180	37/57=0·65	27/30=0·90
	D 10, SL 10–50	SL <0·75×D+122	40/57=0·70	27/30=0·90
	D 0	D >178	16/57=0·28	27/30=0·90
	SL 0–80	SL ≤220	32/57=0·56	27/30=0·90
	D 0, SL 0–80	SL <0·87×D+122	34/57=0·60	27/30=0·90
	D 50	D >35	32/57=0·56	27/30=0·90
	SL 50–70	SL ≤200	20/57=0·35	27/30=0·90
	D 50, SL 50–70	SL <1·59×D+234	31/57=0·54	27/30=0·90
CM5	D 10	D >200	13/57=0·23	28/30=0·93
	SL 10–50	SL ≤190	31/57=0·54	27/30=0·90
	D 10, SL 10–50	SL <0·30×D+165	34/57=0·60	27/30=0·90
	D 0	D >220	12/57=0·21	28/30=0·93
	SL 0–80	SL ≤235	35/57=0·61	27/30=0·90
	D 0, SL 0–80	SL <0·31×D+184	35/57=0·61	27/30=0·90
	D 50	D >90	25/57=0·44	27/30=0·90
	SL 50–70	SL ≤239	25/57=0·44	27/30=0·90
	D 50, SL 50–70	SL <0·54×D+204	27/57=0·47	27/30=0·90

Dt, ST depression in μV t ms after end of QRS.
SL t_1–t_2, ST slope in μV/100 ms measured in interval t_1–t_2 ms after end of QRS.

results were obtained by measurements of SL 0–80 which yielded sensitivities of 0·56 and 0·61 in leads CC5 and CM5, respectively (Table 1). In the testing population the SL 10–50 criterion yielded sensitivities of 0·54 and 0·46 in leads CC5 and CM5, respectively (Table 2).

SX integral

Optimal separation in the learning population between the CAG. POS. and CAG. NEG. group was achieved at a critical value of 8 μV.s for lead CC5 and 10 μV.s for lead CM5. Application of this criterion resulted in a sensitivity of 0·42 and a specificity of 0·93 for the lead CC5 (Fig. 2). These values were 0·32 and 0·90 for the lead CM5. In the testing population the sensitivities were 0·49 using lead CC5 and 0·44 with lead CM5. The specificity was greater than 0·95 in both leads.

Table 2 *Results in test population (N=60) : 39 patients with significant coronary disease (CAG. POS.) ; 21 patients without significant coronary disease (CAG. NEG.)*

Lead	*Criterion*	*Sensitivity*	*Specificity*
CC5	D 10	20/39=0·51	19/21=0·90
	SL 10–50	21/39=0·54	20/21=0·95
	D 10, SL 10–50	25/39=0·64	20/21=0·95
	D 0	18/39=0·46	19/21=0·90
	SL 0–80	19/39=0·49	20/21=0·95
	D 0, SL 0–80	20/39=0·51	20/21=0·95
	D 50	26/39=0·67	20/21=0·95
	SL 50–70	16/39=0·41	20/21=0·95
	D 50, SL 50–70	21/39=0·54	20/21=0·95
CM5	D 10	17/39=0·44	20/21=0·95
	SL 10–50	18/38=0·46	20/21=0·95
	D 10, SL 10–50	20/39=0·51	20/21=0·95
	D 0	17/39=0·44	19/21=0·90
	SL 0–80	17/39=0·44	20/21=0·95
	D 0, SL 0–80	20/39=0·51	20/21=0·95
	D 50	19/39=0·49	20/21=0·95
	SL 50–70	11/39=0·28	20/21=0·95
	D 50, SL 50–70	17/39=0·44	21/21=1·00

Combinations of measurements

Discrimination between CAG. POS. and CAG. NEG. was hereby obtained using a critical value computed through a linear combination of ST slope and ST depression. In the learning population, the best predictions yielded the combination D10, SL 10–50, using as discrimination function SL=0·75×D+122 for CC5 and SL=0·30×D+165 for CM5. This yielded a sensitivity of 0·70 and 0·60, respectively. In the test population these values were 0·64 and 0·51 (Tables 1 and 2, Fig. 3 and 4).

Discussion

During the past decade the diagnostic performance of the exercise electrocardiogram has been increased

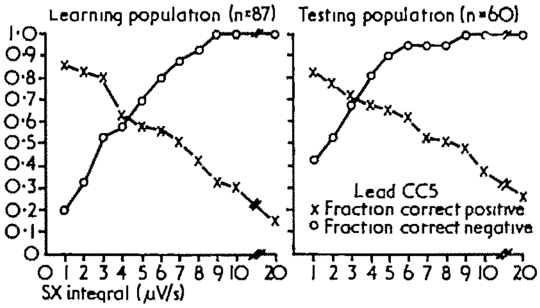

Fig. 2 *Fraction correct positive (sensitivity) and fraction correct negative (specificity) at different values for the SX integral in learning and test population.*

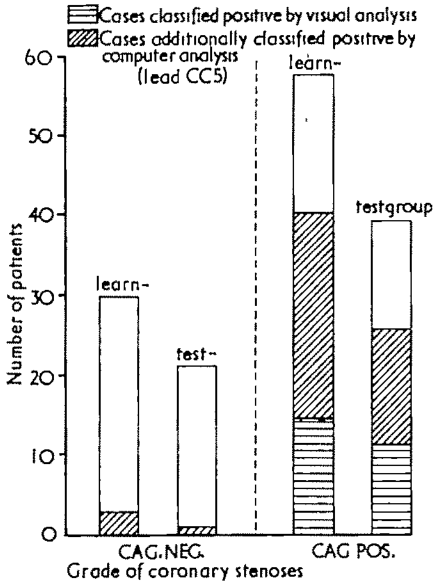

Fig. 3 *Comparison of the diagnostic accuracy of visual and computer analysis. In the visual analysis use was made of the criterion of the ischaemic ST segment; in the automatic analysis a criterion was used based on a combination of ST depression and ST slope (D 10, SL 10–50); see methods.*

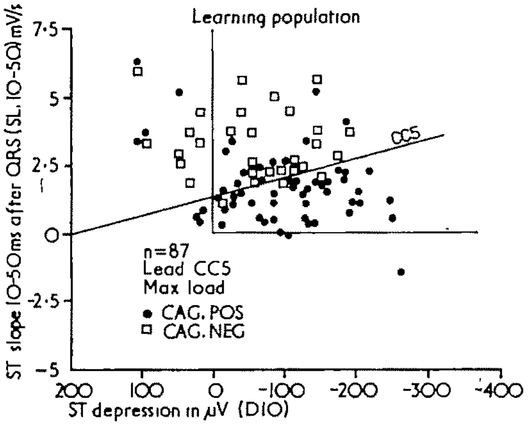

Fig. 4 *Value of the ST depression (D 10) and the ST slope (SL 10–50) in the 87 patients in the learning population during the stage of maximal load. The function of the line for optimal classification is SL=0·75 D+122.*

through the application of heavier work-loads (Mason *et al.*, 1967; Ascoop *et al.*, 1971). To augment further the sensitivity of the test different criteria have been proposed which represent detailed measurements of various characteristics of the ST-T segment. Application of these criteria or less rigid application of the standard criterion (see methods) often enlarges the number of false positive cases (Roman and Bellet, 1965).

The waveform of the ischaemic ST segment is determined on one hand by the consecutive ST vectors and on the other hand by the direction and strength of the lead (Burger *et al.*, 1964). Study of vectorcardiograms during exercise shows that in exercise-induced ischaemia, the endpoints of the ST vectors of the initial part of the repolarisation, shift from left anterior and inferior to right posterior and superior; this shift appeared to be unrelated to the localisation of the coronary stenoses (Ascoop *et al.*, 1974). Similar to the term 'ischaemic' ST segment used in scalar leads, we will use the term 'ischaemic ST vector' for ST vectors directed during exercise in the way described above. An ischaemic ST segment according to the conventional criterion can only occur if these ischaemic ST vectors exist for at least 80 ms and have a magnitude of at least 100 microvolts. As scalar leads such as CM5, CC5, and V5 have lead axes which coincide approximately with these ischaemic ST vectors, those leads are the most sensitive in exercise electrocardiography. Because of the selection criteria of our patients, application of the criterion of the ischaemic ST segment resulted in a low sensitivity in this study. However, it appears that ischaemic ST vectors with magnitudes less than 100 microvolts and correspondingly lower values in the ST segment already have a significant value in the detection of ischaemic heart disease. These measurements are reliable when performed automatically on averaged complexes. This study shows that the use of an ischaemic ST depression of 35 microvolts, 50 ms after QRS, results in sensitivities of 0·56 and 0·67 in the learning and testing population, respectively and in a specificity exceeding 0·90 in both groups. Use of ST depressions of 50 microvolts by visual analysis prove to have low specificity (Mason *et al.*, 1967).

By automatic analysis diagnostic results are considerably better than by visual analysis if new criteria based upon ST slope, ST depression, and SX integral are used. The diagnostic accomplishments found here are, however, only applicable in male patients in whom the repolarisation wave at rest (sitting) is normal.

It appeared that 44 (lead CM5) to 49 per cent (lead CC5) of the CAG. POS. patients in our independent testing population could be detected by analysis of the SX integral. The critical value of the SX integral in our material is 8 µV.s, which is approximately the same value as Sheffield found in his study (Sheffield *et al.*, 1969). In the evaluation of the ST slope, analysis of the initial part of the ST segment yields better results than analysis of the latter part.

A linear combination of ST slope (SL 10–50) and ST depression (D10) proves in this study to be the optimal criterion (see Fig. 3 and 4), yielding sensitivities of 0·70 and 0·64 per cent in learning and testing population, respectively. Good results are also reported by McHenry *et al.* (1972), who used measurements of the initial part of the ST segment; however, because of differences in criteria for patient selection comparison with our results is difficult (McHenry, Phillips, and Knoebel, 1972).

CLINICAL IMPLICATIONS

The fact that use of these new criteria, SX integral, D10, SL 10–50, and D50 both in learning and testing population yields a high sensitivity and specificity makes the application of this quantitative exercise electrocardiography attractive for clinical use. Previous studies show that use of orthogonal leads (X, Y, Z) do not increase the diagnostic value of the exercise electrocardiogram (Distelbrink *et al.*, 1976); it is advisable, therefore, to use leads CM5 and CC5. This has the additional advantage of reduction of the number of electrodes and consequently in reduction of sources of noise. If computer time is limited, recording of resting phase and of the stage of maximal load can be processed off-line. Continuous recordings with on-line processing increase the safety of exercise electrocardiography because the test can then be performed while monitoring the trend of the different measurements in comparison with the new exercise electrocardiographic criteria.

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Lymphatic metastasis in the mitral valve

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The case is reported of a 45-year-old woman with a metastatic tumour within the mitral valve.

Involvement of the heart by metastatic neoplasm is not uncommon. Postmortem studies of patients with malignant disease show that cardiac involvement occurs in up to 21 per cent of cases (Bisel, Wróblewski, and LaDue, 1953). The pericardium, epicardium, and myocardium are the areas of the heart most commonly involved by secondary tumour; spread to the endocardium and heart valves is rare (Coller, Inkley, and Moragues, 1950). We report a case of secondary tumour spread into the substance of the mitral valve; this was a chance finding on histological examination of a surgically removed rheumatic valve.

Case report

A 45-year-old woman presented with the features of mitral valve stenosis. She had had rheumatic fever in childhood and developed progressive dyspnoea in her mid-30s. A closed mitral valvotomy at the age of 39 resulted in conspicuous symptomatic improvement. She remained well for 5 years when increasing dyspnoea, tiredness, and weight loss made her seek medical advice.

On examination she was thin and had a malar flush. The pulse was 70 per minute and regular. Her blood pressure was 130/70 mmHg. There were clinical signs of right ventricular hypertrophy and mitral stenosis. Chest, abdomen, and central nervous system were normal to clinical examination.

Laboratory investigations showed a normal blood picture and liver function. A chest *x*-ray film showed an enlarged left atrium with upper lobe venous diversion. The electrocardiogram showed evidence of right ventricular hypertrophy. An echogram revealed a stenosed, thickened mitral valve. The diagnosis was mitral stenosis with a dilated left atrium and hypertrophied right ventricle and a further operation was advised.

At operation the heart showed only the changes associated with mitral stenosis. Open exploration of the mitral valve showed thickening and calcification of both cusps, with fibrosis and shortening of the subvalvular mechanism. The valve was replaced by a Björk-Shiley prosthesis.

Histological studies were done of the excised valve: routine paraffin sections were prepared from the formalin fixed specimen and stained with haematoxylin and eosin and Machiavello's and the phloxine tartrazine method for inclusion bodies as part of a separate study being conducted into the association of psittacosis and valvular disease.

The valve showed fibrotic thickening with a moderate degree of calcification and several areas of myxoid connective tissue in which were dilated small blood vessels and endothelium lined spaces resembling lymphatics. There were no vegetations and no bacterial involvement. There were two small clumps of neoplastic cells lying within the 'lymphatics', which were present only in two successive sections at one level, which had been stained by the phloxine tartrazine and Machiavello's methods. Numerous further sections were cut but no more tumour was found.

The tumour cells showed considerable nuclear pleomorphism and a high nuclear/cytoplasmic ratio. There was no apparent mucin or pigment production and a diagnosis was made simply of 'poorly differentiated carcinoma'. No attempt was made to restain either of the positive sections.

The possibility that these deposits were 'floaters' was excluded by a careful check on the other specimens cut up and processed at the same time, in none of which was a similar carcinoma processed. Moreover, the appearance of the deposits in two successive sections is not characteristic of an artefact (Fig. 1 and 2).

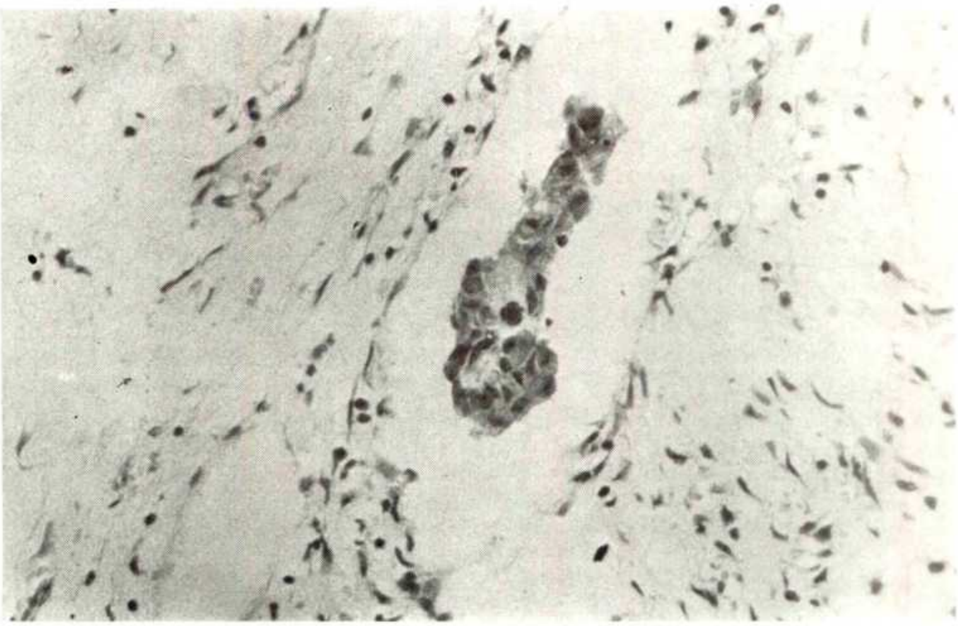

FIG. 1 *One of the two fragments of tumour, lying withina ? lymphatic. (Machiavello's stain. ×260.)*

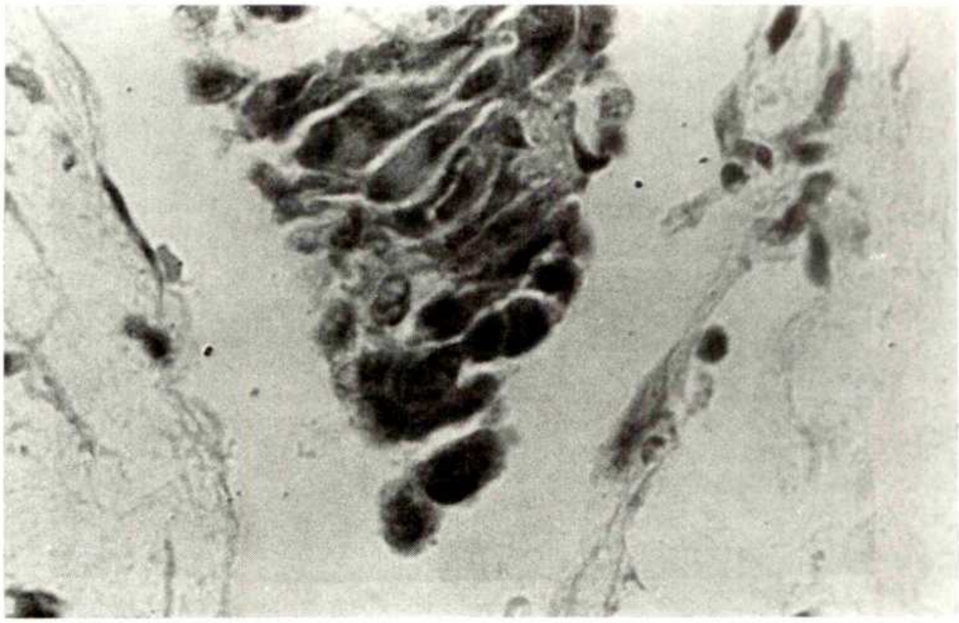

FIG. 2 *Higher power view of the other fragment. (Machiavello's stain. ×640.)*

Further clinical examination and investigations failed to reveal a primary tumour or any other secondary deposits. Of the tumours known to metastasize from occult primary sites, oat cell carcinoma, melanoma, breast, and thyroid tumours were considered most likely. We did not think the histological appearance of the deposits gave any definite indication of the primary source.

The patient made a good postoperative recovery and was allowed home two weeks after operation. She is being followed up in the out-patient clinic and appears to be making good progress.

Discussion

The antemortem histological diagnosis of metastatic spread to a cardiac valve has not been previously described. The antemortem diagnoses of cardiac metastases have been mainly presumptive diagnoses in patients with known malignant disease who develop disorders of cardiac performance and non-specific electrocardiographic abnormalities (Goudie, 1955). Positive histology has been reported in patients with malignant pericardial effusions. Improvement in cardiac performance has resulted from irradiation of hearts involved by malignant disease (Hanfling, 1960); and it may be that radiotherapy will be of use in our patient should she develop a cardiac dysfunction which does not respond to conventional treatment.

The previous reports of secondary spread to cardiac valves were of postmortem cases and showed either direct implantation of tumour on to valve endothelium or infiltration into the valve from neighbouring myocardial deposits (Hanfling, 1960). Clancy and Roberts (1968) reported 2 examples of tricuspid valves involved by malignant melanoma and Roberts, Clency, and DeVita (1968) reported one tricuspid valve involved by lymphoma, but the exact mode of involvement was not specified.

The case described here was one of secondary spread into an endothelium-lined space within a mitral valve and we think that this vessel was a valve lymphatic. However, while the existence of lymphatics in animal atrioventricular valves has been clearly shown, evidence for their existence in human valves is not yet so convincing.

Miller, Pick, and Katz (1961) injected India ink suspension into the atrioventricular valves of beating canine hearts and then subjected the valves to routine light microscopy. They described carbon particles within thin-walled endothelium-lined channels with little surrounding connective tissue. Other workers using India ink, dye, or hydrogen peroxide have reported similar findings (Johnson and Blake, 1966; Ullal *et al.*, 1972b).

Leak and Burke (1966) described the electron microscopical features of amphibian and mammalian lymphatics, which have neither basement membrane nor condensed connective tissue support but were recognizable by the presence of 'half desmosomes'—fibrillary structures appearing to anchor the endothelium directly to the surrounding connective tissue. Bradham, Parker, and Greene (1973) using these criteria demonstrated lymphatics in canine atrioventricular valves with electron microscopy.

Studies in human valves have met with less success. Eberth and Belajeff reported lymphatics in human cardiac valves in 1866. Johnson and Blake (1966) also reported lymphatics in two human mitral valves.

Reading the papers cited leads us to believe that lymphatics are present in animal and human atrioventricular valves mainly on the atrial surface and that their number and appearance may vary with disease and age.

In our case we found tumour in thin-walled endothelial tubes without connective tissue support or a clear basement membrane. This, coupled with the less reliable criterion of a complete lack of blood cells in numerous sections at different levels, led us to believe that these channels were lymphatics.

We have noticed numerous and varied vascular channels in many diseased valves removed surgically but have not yet had the opportunity of subjecting them to electron microscopy.

Kline (1972) thought that lymphatics were an important pathway for secondary tumour spread to the heart. He found the mediastinal lymph nodes were almost always involved by tumour and subsequent retrograde lymphatic spread of tumour to the heart resulted in lymphatic obstruction. The appearance of secondary tumour in dilated lymphatics which he described resembles the picture in our case. He did not, however, describe valve involvement.

The effect of obstruction to the cardiac lymphatics has been studied in animals (Ullal, Kluge, and Gerbode, 1972a; Miller, Pick, and Katz, 1963). Impairment of myocardial function has been noted. Increased fibrosis in the endocardium has been reported. Fibrosis and myxomatous changes in the atrioventricular valves of dogs has followed ligation of the cardiac lymphatics.

The place of lymphatic obstruction in human cardiac disease is conjectural. It has been suggested as a cause of myocardial damage in rheumatic carditis. Myxomatous degeneration of the mitral valve and endocardial fibrosis have also been linked with lymphatic obstruction.

It is possible that lymphatic obstruction contributed (to a minor degree) to the fibrosis seen in this patient's mitral valve.

We thank Mr. G. H. Smith and Dr. A. J. N. Warrack for their help in preparing this report.

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Bradycardia-dependent interatrial block with retrograde left atrial activation

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A patient with a peculiar interatrial block is reported. The electrocardiogram showed a short PR interval and negative P waves in II, III, and aVF, which were preceded, 0·07 s earlier, by another positive P wave present in the right praecordial leads which were absent in the limb leads.

From the study with His bundle electrograms, high right atrial electrograms, and bipolar oesophageal electrocardiograms, it could be proved that atrioventricular, His-Purkinje, and right intra-atrial conduction were normal, and that P waves recorded in limb leads represented left atrial depolarization; whereas the ones in the right praecordial leads corresponded to right atrial activation.

The vectorial analysis from both P waves and atrial potentials showed that the left atrium was activated in a retrograde fashion, because of an interatrial block. This block was bradycardia dependent and it disappeared in the cycles shorter than 800 ms.

Interatrial block is an electrocardiographic entity whose features are dependent upon its severity, ranging from an abnormal widening of the P waves (Bekheit *et al.*, 1972), to the existence of two P waves with different rates, reflecting an independent pacemaker for each atrium, one of them being the main pacemaker of the heart (Cohen and Scherf, 1965).

At present, there are two theories to explain the activation of the atria: Lewis (1925) thought it was a sequential and circumferential process; later it was considered that the activation process occurred through specialized pathways (Wenkebach, 1907; Thorel, 1910; Bachmann, 1916; James, 1963). In accordance with the latter theory, the injury of the specialized pathways would produce intra-atrial and interatrial blocks of different types, the injuries to Bachmann's bundle would be the commonest explanation for the delay in the impulse reaching the left atrium.

A patient is reported with an interatrial block in which the left atrium was activated retrogradely from the lower aspects of the right atrium, with a considerable delay.

Case history

A 67-year-old man complained of dizziness and mental torpor, occurring three months before his admittance to hospital. He described a past history of palpitations but his basal pulse rate was between 35 and 60 beats/min. Physical examination, chest *x*-ray examination, and standard laboratory tests were normal. Several electrocardiograms showed nodal rhythm, sometimes with very slow rate. The diagnosis of 'sick sinus syndrome' was made and the patient sent to La Paz Hospital.

Surface electrocardiograms, bipolar oesophageal electrocardiogram, bipolar high right atrial electrograms, and His bundle electrograms were performed. Because of technical problems during the His bundle electrogram study it was impossible to perform atrial pacing. As the patient continued with frequent spells of dizziness, a ventricular demand pacemaker was implanted.

Electrocardiogram

The P waves in the basal electrocardiogram were: negative in II, III, aVF; positive in V1, V2, and V3; biphasic (+ —) in V4 and V5; and flattened in I and V6. The QRS complex, T waves, and ST segment were normal. The PR interval in lead III measured 0·08 s and in V1 0·14 s. Simultaneous recordings of leads I, II, III, and V1 showed that the P wave in right praecordial leads (Pp) preceded the P wave in standard leads (Ps) by 0·06–0·08 s. When PP intervals shortened, Ps changed to positive and Pp and Ps began simultaneously (Fig. 1A and 1B).

His bundle electrogram and high right atrium

The His bundle electrogram was recorded using the technique described by Scherlag *et al.* (1969), a tripolar catheter with an interelectrode distance of 10 mm, connected to a junction box (keyboard switch box-Siemens Elema), connected in turn to an Elema Schonander Mingograph 81 recorder. The tracing was recorded at 100 mm/s. The high right atrial electrogram was obtained with the same catheter, placing the tip in the lateral and superior aspects of the right atrium.

High right atrial recordings showed that the beginning of Ps in lead III was preceded by the atrial potential (A) by 75 ms. The interval between A and the end of Ps measured 120 ms. The interval between the end of Ps and Q wave was 25 ms. When the AA cycles measured 800 ms or less, Ps polarity changed from negative to positive, and A was recorded 10 ms, before onset of the P wave. The interval between A and the end of P wave was 80 ms, and the interval between the end of the P wave and the Q was 60 ms (Fig. 2A).

In the His bundle electrogram, the AH interval measured 90 ms, and the HV 50 ms. When the AA interval shortened, the AH lengthened slightly, while the HV did not change. The interval between low right atrial potential and Ps wave was 70 ms in the longer cycles (Fig. 2B).

Bipolar oesophageal electrogram

During recording, though ventricular premature beats appeared, the negative P waves of the supraventricular complexes in leads II, III, and aVF coincided with the positive potential in the electrogram.

Discussion

The standard electrocardiogram can be inadequate in many cases when used as the sole means to study the place where the P waves originate, and

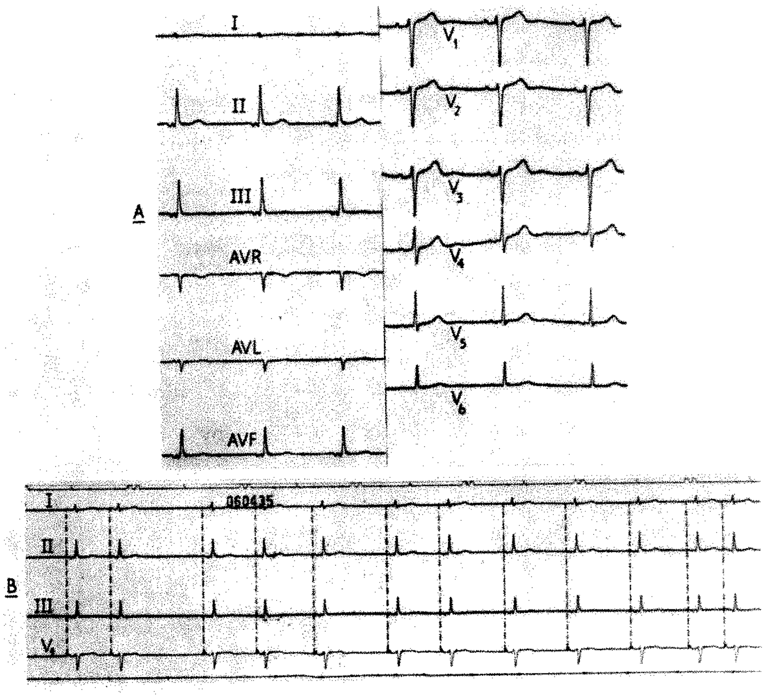

FIG. 1 *(A) Electrocardiogram showing basal rhythm (see text). (B) Electrocardiogram showing simultaneous recordings of leads I, II, III, and V1. The P wave in V1 precedes the P wave in limb leads by 0·06 to 0·08 s, when PP cycles range between 1600 and 960 ms. In the second and last beats with preceding PP cycles of 800 and 620 ms the P wave in limb leads in positive and simultaneous with the P wave in V1. The P wave is flat in I, II, and III in beat 4, with a PP cycle of 920 ms (paper speed 24 mm/s).*

more sophisticated studies will be needed. In our case, the standard electrocardiogram led us to suggest the existence of a nodal rhythm. However, in a retrospective electrocardiographic study performed after His bundle electrograms, it was clear that the P waves in limb leads were preceded by another P wave only recorded in praecordial leads.

The negative P waves in II, III, and aVF (Ps) represented left atrial activation resulting from the following facts: in the basal rhythm the Ps coincided with the atrial potentials in bipolar oesophageal electrogram, and were preceded by 75 ms by the right intra-atrial potentials. On the other hand, the positive P waves in the right praecordial leads (Pp) preceded the Ps by 0·06–0·08 s and, therefore, the Pp should correspond to the A potential in the high right atrium or His bundle electrogram. The axis of Ps wave (âP = −90°), the positive deflections in the bipolar electrogram, and the short PR, pointed to a left atrial activation occurring from below, and a right atrial activation mainly forward (Pp was positive in leads V1 and V2 and not evident in the limb leads). The atrioventricular node and left atrial activation originated from the right atrial pacemaker because all the H potentials and Ps waves were preceded by A potentials, and when the rate increased, the AH lengthened.

The right atrial activation could originate in the sinus node or in a high right atrial pacemaker, but could not result from a nodal or low atrial rhythm, since AH was not short and in nodal or low atrial rhythms the activation of both atria must be simultaneous (Massumi *et al.*, 1969).

Waldo *et al.* (1971), after producing a selective lesion in Bachmann's bundle in dogs, obtained wide, flat P waves with a negative second half in limb leads, very similar to the ones found in our patient. Retrograde left atrial activation probably was made from a low interatrial pathway. Scherlag, Yeh, and Robinson (1972) have proved, in dogs, the existence of this pathway, joining the inferior aspects of the right atrium and left atrium.

The changes in Ps polarity, returning to normal when AA cycles shortened, could be produced by an atrial focus, different from the one responsible for the basal rhythm. However, as all the A deflec-

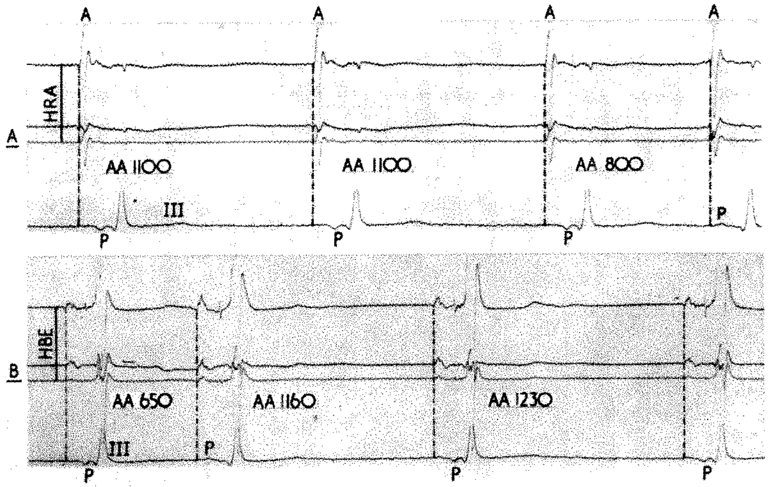

FIG. 2 *(A) High right atrial electrogram (HRA) and lead III: P wave is negative in the first three beats and turns to positive in the last one; however A potential has the same morphology and amplitude in all the cycles. This A potential precedes the P wave by 75 ms in the first three cycles, and by 10 ms in the last cycle. In the latter the preceding AA interval is shorter (paper speed 100 mm/s). (B) His bundle electrogram (HBE) and lead III: beats 1, 3, and 4 with long AA cycles, show negative P waves, an AH interval of 90 ms, and HV interval of 50 ms. The low atrial potential (A) precedes the P wave by 70 msec. In beat 2 with a preceding AA cycle of 650 ms, an AH interval of 110 ms and an HV interval of 50 ms, the A potential is simultaneous with the theoretical onset of the P wave which becomes positive (paper speed 100 mm/s).*

tions had the same shape and amplitude, they probably originated in the same pacemaker or one close by. On the other hand, even if there were two right atrial foci, the differences in width and shape of the P wave could not exist with an intact interatrial conduction system (Waldo *et al.*, 1970, 1971) and so the obvious changes in the P wave have to be ascribed to an intermittent interatrial block related to the heart rate.

There are several reports proving the existence of bradycardia-dependent bundle-branch block. The mechanism of this type of block has been related to the phase 4 (Rosenbaum *et al.*, 1973). Though bradycardia-dependent interatrial blocks have not been reported, Childers, Merideth, and Moe (1968) showed, in dogs, the existence of a supernormal conduction phase in Bachmann's bundle, and Agha *et al.* (1972) proved the existence of a supernormal intra-atrial and interatrial conduction in 5 patients by atrial pacing with a cycle length of 500 to 600 ms. In our case the disappearance of the interatrial block with AA cycles of 800 ms or less, and its presence in the basal rhythm with longer AA intervals, suggest the existence of a bradycardia-dependent Bachmann's bundle block. This was probably related to the phase 4 of the depolarization, even though the presence of phase-4 in Bachmann's bundle has not been shown yet.

As well as the electrophysiological data, we think that this report has clinical implications because of the possibility that some cases thought to be nodal rhythms in the electrocardiogram might correspond to interatrial block with retrograde left atrial activation.

We wish to thank Martin L. Schwartz for his assistance.

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Requests for reprints to Dr. José A. Sobrino, Hilarion Eslava-55, Madrid-15, Spain.

Obituary

British Heart Journal, 1977, **39**, 226

Sujoy B. Roy

Dr. Sujoy B. Roy, an eminent cardiologist, died on 25 March, 1976, in New Delhi after a brief illness. He is survived by his wife.

Born in Burma, Dr. Roy, after a brilliant academic career at Rangoon University, completed his postgraduate studies at Edinburgh and Boston. While he was on the faculty of Harvard University, the late Rajkumari Amrit Kaur, then Health Minister of India, asked him to come to India to head the newly created Department of Cardiology at the All India Institute of Medical Sciences, New Delhi.

Apart from training a number of students in cardiology, Dr. Roy made a significant contribution towards the understanding of rheumatic fever and rheumatic heart disease in India. His work on high-altitude cardiorespiratory problems, which helped in the maintenance of troops in the Himalayas, has been widely acclaimed. He was a senior fellow of the Armed Forces Medical Research Council and a member of the Cardiovascular Expert Committee of the World Health Organisation.

He published over 150 scientific papers in national and international journals.

Dr. Roy was the recipient of numerous national and international awards. To mention a few, the Amir Chand Basanti Award, the Massachusetts Heart Fellowship, and the FICCI Award, 1976, for contributions to life sciences, including agriculture. He was awarded the Padmabhushan, one of the highest awards, by the President of India.

He will be missed by his numerous colleagues in this country and abroad and by the large number of students he trained in cardiology.

K. K. DATEY

Correspondence

British Heart Journal, 1977, **39**, 227–228

Short-acting and long-acting quinidine for maintenance of sinus rhythm after electrical conversion

The following two letters have been received regarding the article by Normand *et al.* (*British Heart Journal*, **38**, 381).

Sir,

Most clinicians like me are happy to use any drug measurable quantitatively in the blood. I was therefore quite amazed to read in the article by Normand *et al.* that the authors did not mention any quinidine concentration in the blood, an easily obtainable value which is indispensable for the results published. Normand *et al.* have certainly great faith in the adherence to medical treatment with possible gastrointestinal side-effects in their Parisian countrymen.

R. J. A. F. Vroom,
101 Aarle-Rixtelseweg,
Helmond,
Holland.

Sir,

Normand *et al.* concluded that long-acting quinidine preparations are more effective than short-acting quinidine for maintenance of sinus rhythm after electrical conversion of atrial fibrillation. They reasoned that quinidine blood level determinations were not necessary in performing their study. Though this conclusion seems to be a controversial decision, it was at least considered. No consideration was given to the return of mechanical function of the atria after electrical cardioversion. Mahlich *et al.* (1973) showed that after electrical conversion there might be no return of mechanical function to either right or left atrium, or no return of mechanical function to both atria. The more complete the return of atrial mechanical function the more likely long-term sinus rhythm would follow. Similar correlations of return of mechanical function with maintenance of long-term sinus rhythm after cardioversion for chronic atrial fibrillation were made by Khaja and Parker (1972). Sasse (1974) showed that echocardiography of the posterior left atrial wall could be used to determine the return of left atrial mechanical function after cardioversion, and Mahlich *et al.* (1973) used kinetocardiography to establish the return of right and/or left atrial mechanical function. Jugular venous pulse tracings may also be used to establish right atrial mechanical function. All these determinations are noninvasive and easy to perform.

It seems that before the efficacy of various quinidine preparations in maintenance of sinus rhythm after cardioversion for atrial fibrillation can be ascertained, the return of mechanical atrial function in differently treated groups of patients must be determined and assigned equally to the groups being compared.

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Khaja, F., and Parker, J. O. (1972). Hemodynamic effects of cardioversion in chronic atrial fibrillation. *Archives of Internal Medicine*, **129**, 433–440.

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These letters were shown to Dr. Normand and his co-authors who reply as follows.

Sir,

(1) In a previous study, it was shown that the blood quinidine levels obtained with the two preparations are comparable at equal dosage (Renais *et al.*, 1971). With a daily dose equivalent to 0·66 g quinidine base (as used in our study) the mean quinidine blood level was 3 mg/l, i.e. in the therapeutic range.

(2) As already pointed out in our Discussion (p. 385), previous studies have shown that the blood quinidine level did not differ significantly whether sinus rhythm was maintained or atrial fibrillation

returned (Byrne-Quinn and Wing, 1970; Hillestad *et al.*, 1971).

(3) Determination of blood quinidine level at a given moment of the treatment did not guarantee the patient's strict adherence to the treatment. Only by measuring the blood quinidine level at the moment of the relapse could it be proved whether or not the relapse was due to an interruption of the treatment.

(4) We took into account the consistence with which the patients followed their treatment and this shows convincingly that the patient's adherence to treatment was much better when long-acting quinidine was prescribed.

In acknowledging Dr. Sassé's comments we should point out that our goal was to compare the efficacy of two quinidine preparations and not to identify patients who are likely to remain in sinus rhythm after electroconversion for atrial fibrillation.

To date there is some evidence that atrial electromechanical dissociation carries a poor prognosis for the maintenance of sinus rhythm (Khaja and Parker, 1972; Mahlich *et al.*, 1973; DeMaria *et al.*, 1975). The fact that in our study long-acting quinidine was more effective than short-acting quinidine in preventing late relapses of atrial fibrillation obviously cannot be explained by a lower incidence of non-restored atrial contraction in the first group for the following reasons:

(1) Patients were assigned at random to short- or long-acting preparation. This offers the best guarantee of similarity between the two groups which in addition was confirmed on 13 points of comparison.

(2) Furthermore it has been shown recently that, in nearly all patients with atrial fibrillation without mitral valve disease—as in our study—cardioversion promptly (within 1 hour) restored effective atrial contraction (DeMaria *et al.*, 1975).

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Correspondence

British Heart Journal, 1977, 39, 229–231

The natural history of rheumatic aortic regurgitation and the indications for surgery

Sir,

Smith *et al.* (1976) (*British Heart Journal*, **38**, 147) in a recent article in the Journal painted a pessimistic picture of the prognosis in aortic regurgitation and consequently advocated early aortic valve replacement. This represented an opposite view to that expressed in two communications from our department (Goldschlager *et al.*, 1973; Selzer, 1976). No one questions the poor prognosis of patients with serious disability, namely aortic regurgitation in functional classes III and IV. The point at issue is the management of patients without disability or with mild disability (functional classes I and II), who constituted about 50 per cent of those undergoing valve replacement in Smith *et al.*'s series (53 out of 110). In disabled patients valve replacement is a remedial operation; in those with minor or no disability it is largely a prophylactic operation.

Prophylactic operations require adequate knowledge of the natural history of the disease treated surgically in order to make a reasonable estimate of the risk-benefit ratio. This is particularly important in the case of valve replacement operations, in view of the uncertainty about the long range fate of the prosthesis or homograft and (in the case of aortic regurgitation) the young age of many patients. In the authors' series 22 patients died without operation; these patients showed a significantly higher incidence of heart failure, cardiomegaly (by radiography), excessive left ventricular hypertrophy by electrocardiography, and arrhythmias than survivors. This is not a finding that would surprise anyone; however, the number of fatal cases is small and no attempt has been made to analyse these 'unfavourable' signs as independent variables adversely affecting the prognosis. Thus, it is not valid to conclude that these findings represent indications for valve replacement.

It should be pointed out that the study by Goldschlager *et al.* (1973), which was a combined prospective and retrospective review of the natural history of aortic regurgitation based on clinical and haemodynamic evaluation, showed the benign and non-progressive nature of aortic regurgitation in young subjects. Cardiac failure and disability was seldom noted before the fifth decade of life. This finding not only was not refuted by the authors, but was not even mentioned, simply ignored. Yet Smith *et al.* report valve replacement in 70 patients under the age of 40, out of 110 in their series.

It is also necessary to emphasize that the material examined by Smith *et al.* consisted of 31 per cent patients of Polynesian race. The presence of an accelerated form of rheumatic heart disease in the developing countries and primitive populations is now well established (Selzer and Cohn, 1972); the possible role of excessive early valve damage, its rapid progression, and continuation of active rheumatic carditis as causes for the unfavourable course of some patients has to be given serious consideration. It is likely that rheumatic aortic regurgitation may take a more benign course in Western populations.

The authors' advocacy for early valve replacement thus is based on opinion rather than reasonably projected or scientific evidence. Is it justified to place an aortic homograft valve in a 25-year-old asymptomatic patient, because he happens to have a cardiothoracic ratio above 0·60? The authors apparently believe that it is; however, one would expect at least some reference to the fact that there is controversy on this point and that opposite views can be derived from other studies.

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Selzer, A., and Cohn, K. (1972). Natural history of mitral stenosis. A review. *Circulation*, **45**, 878.

This letter was shown to the authors of the paper who reply as follows:

Sir,

It is not easy to reply to a critic who rejects the evidence on which the conclusions of a paper are based, simply by denying that it is evidence. But how does one decide if a factor, for example a cardiothoracic ratio of given magnitude, is associated with an unfavourable prognosis and should be an indication for aortic valve replacement? Presumably by showing a statistical association between the factor and death without operation, a higher incidence of complications at operation, or an unsatisfactory outcome despite a satisfactory operation. This was the aim of our paper and despite the relative crudity of the methods of assessment, correlation with outcome was surprisingly good. For example there was an increase in death rate when the cardiothoracic ratio reached 0·60. A cardiothoracic ratio of 0·65 or more was apparently associated with an increased incidence of unsatisfactory outcome after successful surgery, probably because of irreversible myocardial disease. We know of no other way to 'analyse these unfavourable signs as independent variables adversely affecting the prognosis'. We did, however, also attempt to assess the interrelation of the factors by extracting principal components and applying the technique of discriminant analysis, using an I.B.M. 360 computer programme. This analysis was carried out for us by Mr. C. D. McNickle of the Mathematics Department of the University of Auckland. These data were not reported because we concluded that a minimum of 2000 patients would be required for a valid assessment. Obviously the 'perfect' natural history study where large numbers of patients are followed to their death and analysed in this way will never be undertaken, and we are forced to base our judgments on the material available.

We must freely admit to having 'ignored' the report by Dr. Selzer and his colleagues, together with many other excellent studies on the subject of aortic regurgitation. Despite the wealth of detail in the study of Goldschlager *et al.* we did not feel that its design permitted conclusions about the timing of surgery for the following reasons:

(1) It included patients with moderate as well as those with severe aortic regurgitation. Because the prognosis of patients with moderate aortic regurgitation is extremely good we believe serious errors of interpretation arise from combining the two groups. Because of variation in systemic arteriolar resistance we do not believe the ratio of pulse pressure/systolic pressure, as used in Goldschlager's paper, separates moderate from severe regurgitation in a satisfactory fashion: indeed with the criteria employed, some patients *in extremis* with aortic regurgitation would have to be classified as mild. The difference in mortality of patients under observation in Goldschlager's group (6 per cent) and in our own group (12 per cent) probably results from the difference in selection. As mentioned in our paper, we found no evidence that Polynesians with isolated aortic regurgitation behaved differently from Caucasians though we could not deny the possibility that the factors operating 'in developing countries and primitive populations' might apply to our whole community!

(2) The paper did not consider the outcome of patients undergoing valve replacement.
We do not, of course, deny the prolonged survival of many patients with severe aortic regurgitation and indeed emphasised this in our paper. The gradual change in clinical status with time, emphasised by Goldschlager *et al.*, is further shown in the Fig. In patients under observation without (or before) surgery the mean age of those classed as good was 21·1 years and of those classed as poor 37·8 years. It is noteworthy, however, that the mean age of those who died, 31·6 years, was similar to the overall mean of 30·6 years. In other words death occurred at any age and, furthermore, without regard to symptoms other than those labelled 'heart failure'.
In the interests of brevity the status of patients undergoing valve replacement was presented in somewhat perfunctory fashion. Although 10 patients were in Class I and 44 in Class II at the

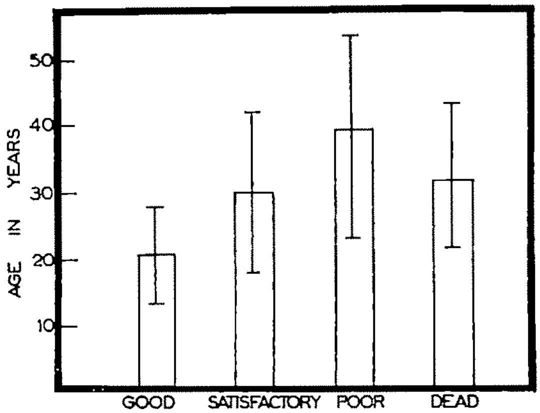

Fig. *Relation between age and symptomatic status. Ages shown are means ±1 standard deviation. Good, class I; satisfactory, class II; poor, classes III and IV.*

time of preoperative assessment, many had experienced symptoms earlier but had responded to restriction of activities and to treatment with digitalis and diuretics. The limitations of this form of classification are well recognized (Selzer and Cohn, 1972). Even so there is a small group of patients who underwent aortic valve replacement in the mid 1960's in whom we would now postpone operation, even though the gain in most cases would only be a year or two. We emphasise that we agree entirely with Dr. Selzer that patients with aortic regurgitation should be managed conservatively as long as is compatible with reasonable safety. On the other hand, we must apply the lessons learned from those patients who have died while under observation, and attack the problems so well described by Goldschlager *et al.* 'The late appearance of clinical disability at a stage when irreversible myocardial damage may be present imposes, at present, an insoluble therapeutic dilemma with regard to the timing of surgical treatment'.

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J. M. Neutze,
A. H. G. Roche,
T. M. Agnew,
B. G. Barratt-Boyes,
Green Lane Hospital,
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Reference

Selzer, A., and Cohn, K. (1972). Functional classifications of cardiac disease: a critique. *American Journal of Cardiology*, 30, 306.

VIII World Congress of Cardiology

The eighth World Congress of Cardiology will be held in Tokyo from 17 to 23 September 1978, at Hotel New Otani, Akasaka Prince Hotel, Tokyo, Japan.

Further information regarding registration, etc., can be obtained by writing to the Secretariat, Organizing Committee, VIII World Congress of Cardiology, 7–3–23, Roppongi, Minato-ku, Tokyo 106, Japan.

Correspondence

British Heart Journal, 1977, **39**, 232

Cardiac arrhythmias induced by hypokalaemia and potassium loss during maintenance digoxin therapy

Sir:

I would like to make two observations about the interesting paper by Steiness and Olesen (*British Heart Journal* (1976), **38**, 167).

Both premature ventricular and atrial contractions are commonly seen, even in asymptomatic patients, during continuous cardiac monitoring in the absence of hypokalaemia and digoxin toxicity (Hinkle *et al.*, 1969). Since similar arrhythmias were ascribed to digitalis toxicity and hypokalaemia in Dr. Steiness's study, it is unfortunate that a control period of monitoring before withdrawal of potassium supplements and/or a period of monitoring during reintroduction of potassium was not included in the experimental design.

The postulated increase in K^+ gradient between the intracellular and extracellular compartment would be more likely to reduce automaticity rather than increase it as suggested by the authors, since in the absence of alteration of K^+ permeability, which may occur with hypokalaemia (Carmeliet, 1961), this change would lead to hyperpolarization. Such a change might precipitate arrhythmias by encouraging re-entry.

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Carmeliet, E. E. (1961). The potassium and chloride permeability in Purkinje fibres. In *The Specialised Tissue of the Heart*, pp. 108–114. Ed. by A. Paes de Carvalho, W. C. deMello, and B. F. Hoffman. Elsevier, New York.

Hinkle, L. E., Carver, S. T., and Stevens, M. (1969). The frequency of asymptomatic disturbances of cardiac rhythm and conduction in middle-aged men. *American Journal of Cardiology*, **24**, 629–650.

This letter was shown to Drs Steiness and Olesen who reply as follows:

We welcome Dr. Hall's comments and forward the following reply:

As a baseline, our patients had a 24-hour period of close observation before withdrawal of potassium. The arrhythmias described are those developing during the period of metabolic balance study.

We agree that the increased K^+ gradient between the intracellular and extracellular compartments during hypokalaemia leads to hyperpolarisation of the cells. There is evidence that in this setting the slope of the diastolic depolarisation is enhanced leading to increased automaticity of pacemaker fibres (Gettes and Surawicz, 1968; Vassalle, 1965). On the other hand, the precipitation of arrhythmias resulting from an accelerated re-entry mechanism is not excluded.

Eva Steiness and
Knud H. Olesen,
Rigshospitalet,
University Hospital,
9 Blegdamsvej, Copenhagen,
Denmark.

References

Gettes, L. S., and Surawicz, B. (1968). Effects of low and high concentrations of potassium on the simultaneously recorded Purkinje and ventricular action potentials of the perfused pig moderator band. *Circulation Research*, **23**, 717–729.

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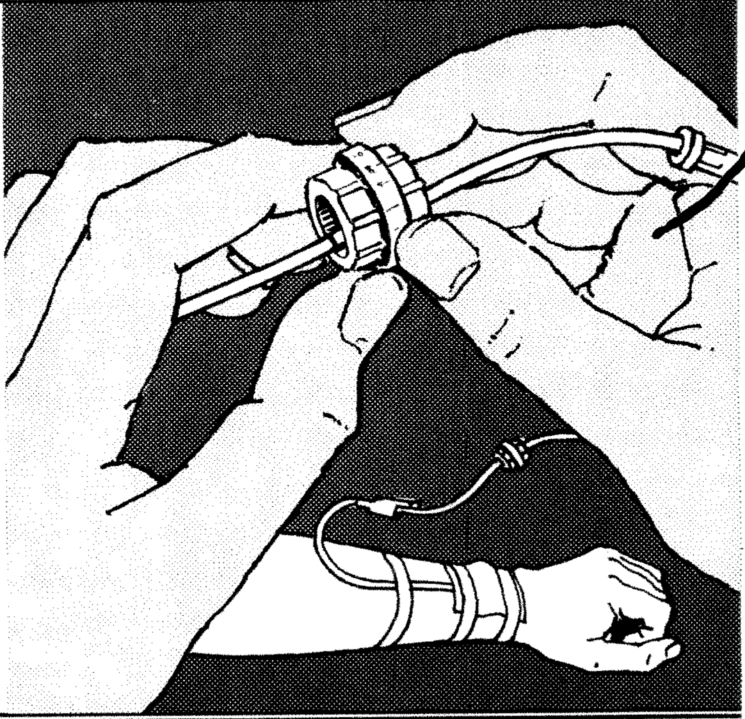

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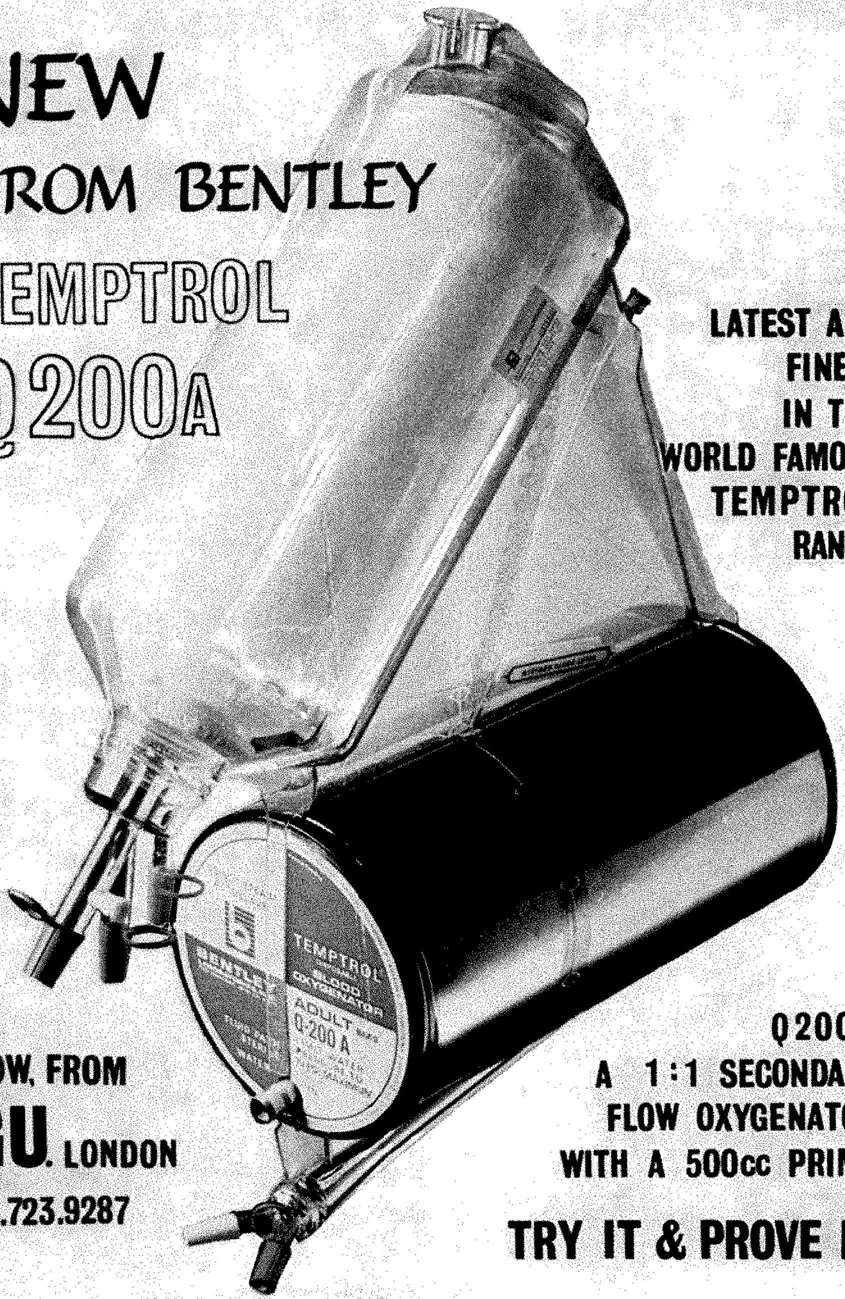

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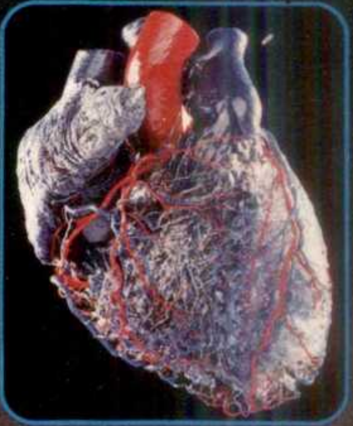

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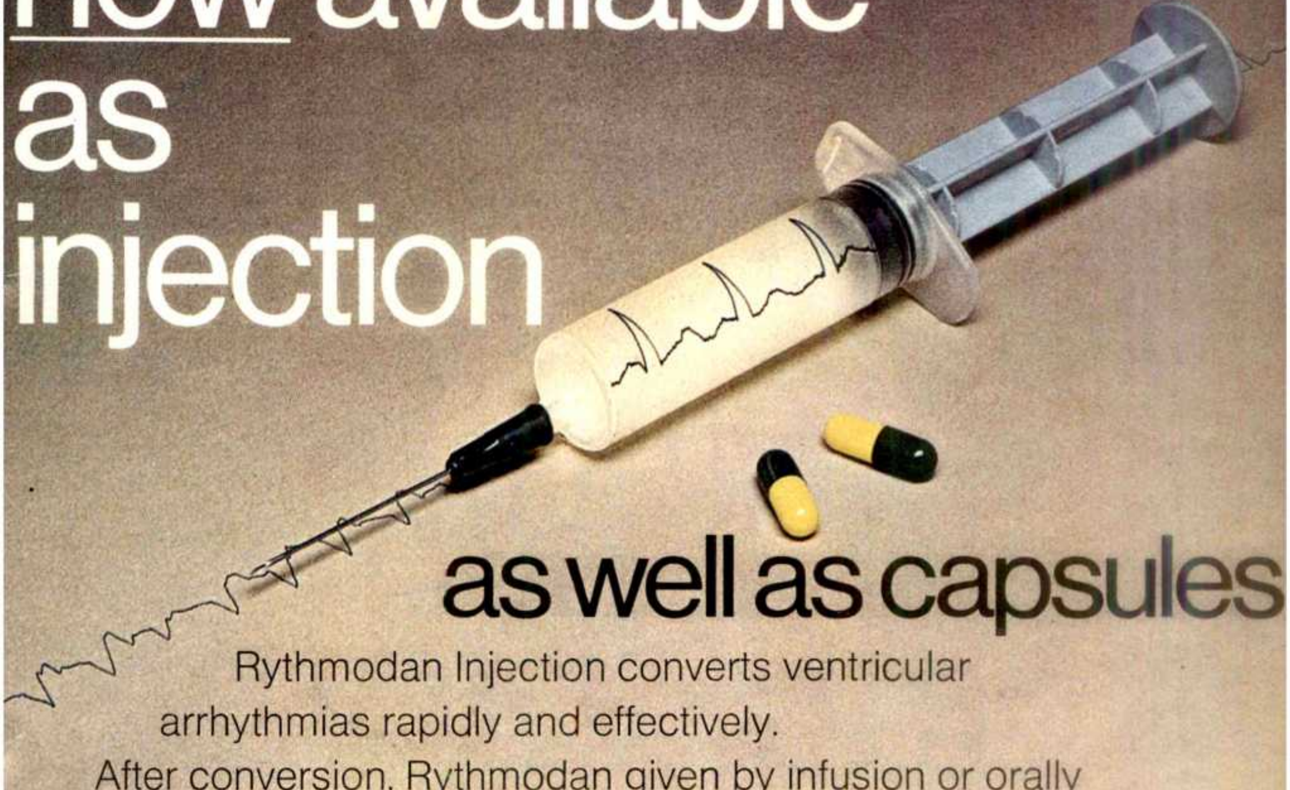

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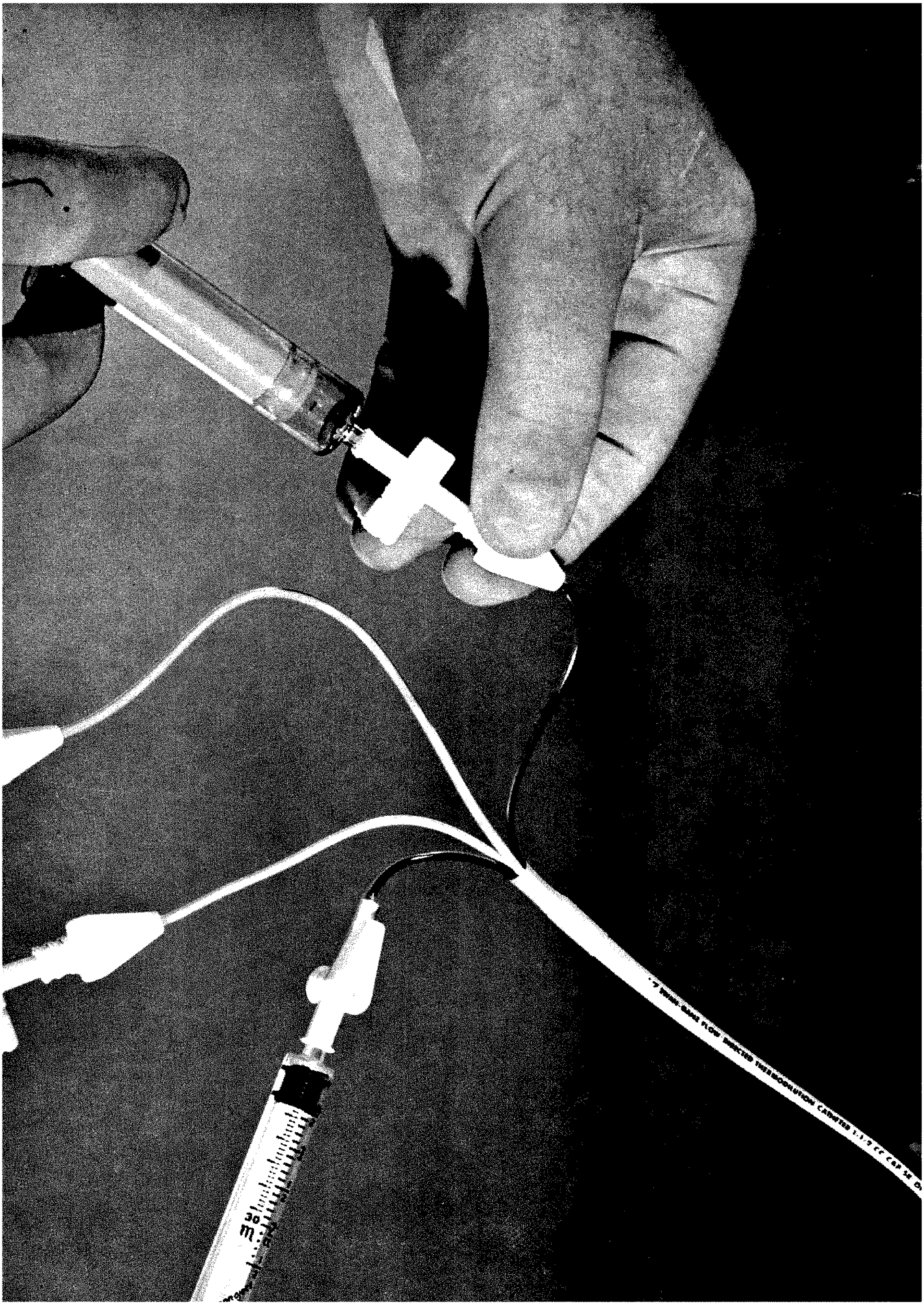
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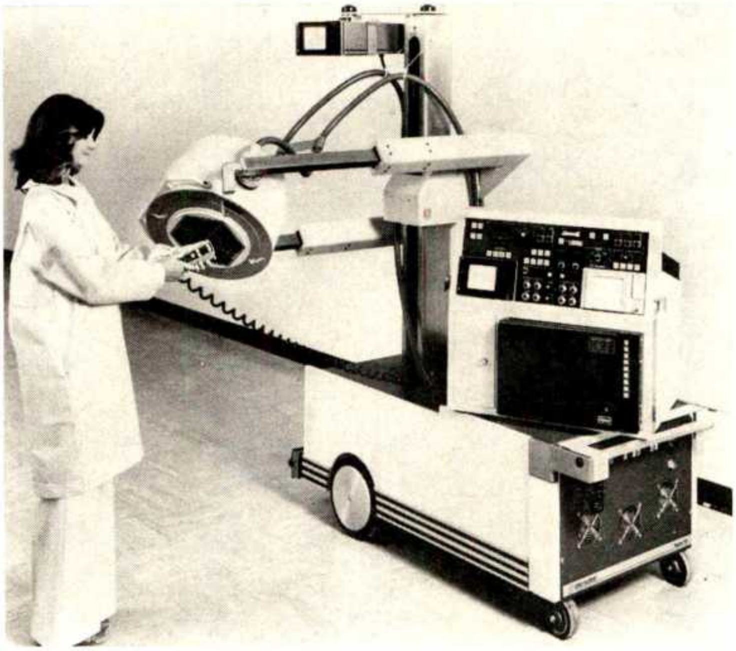

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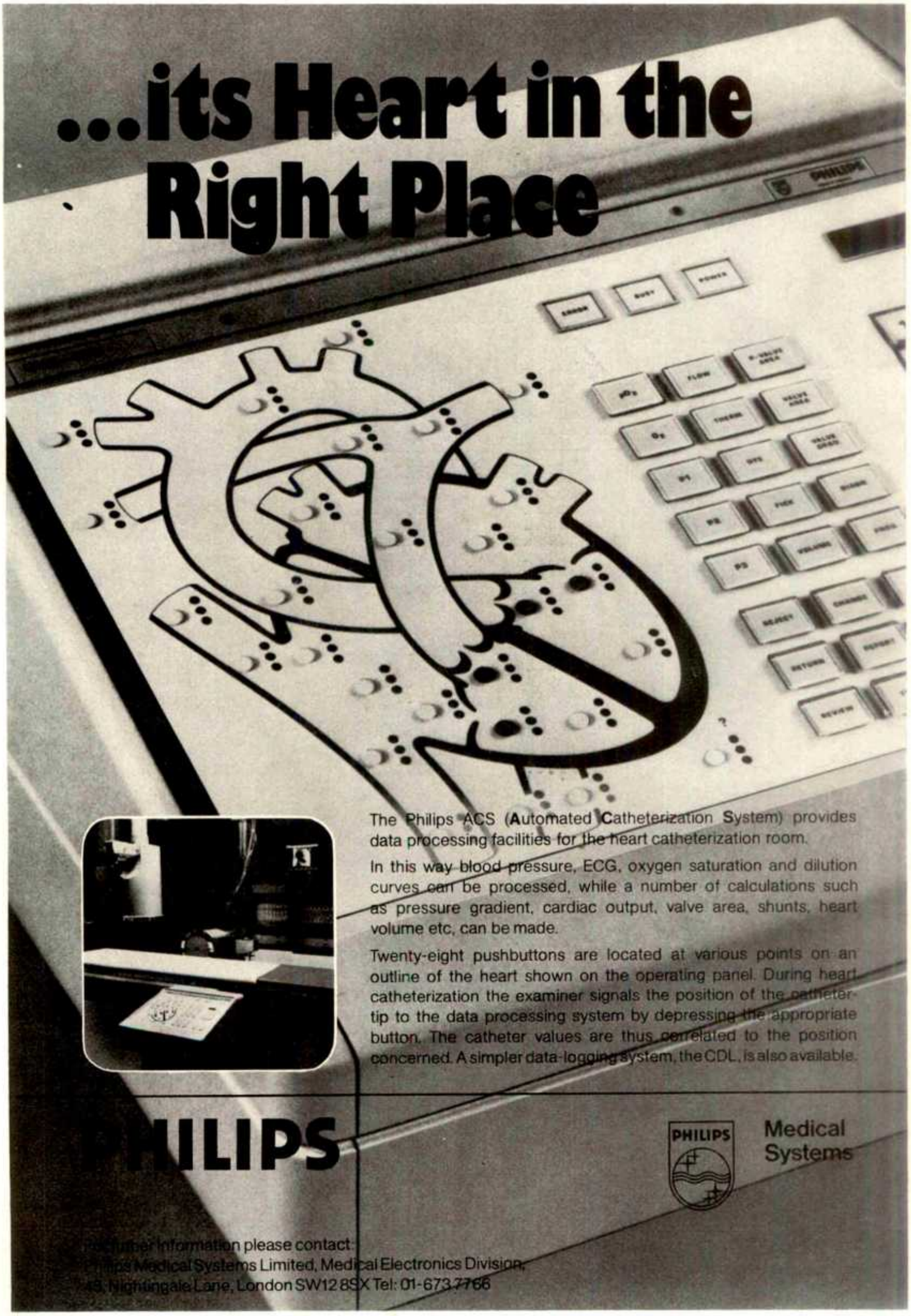

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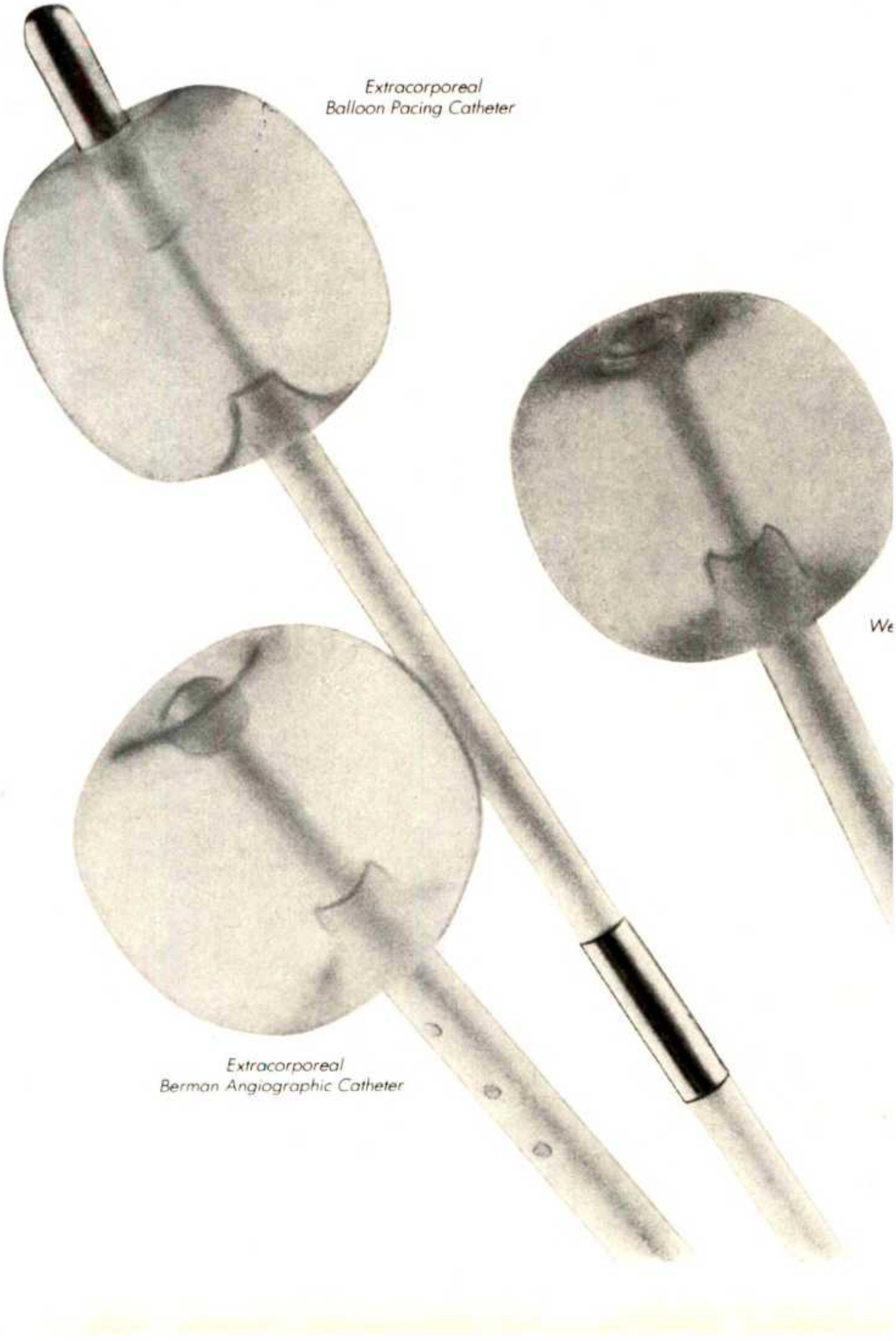

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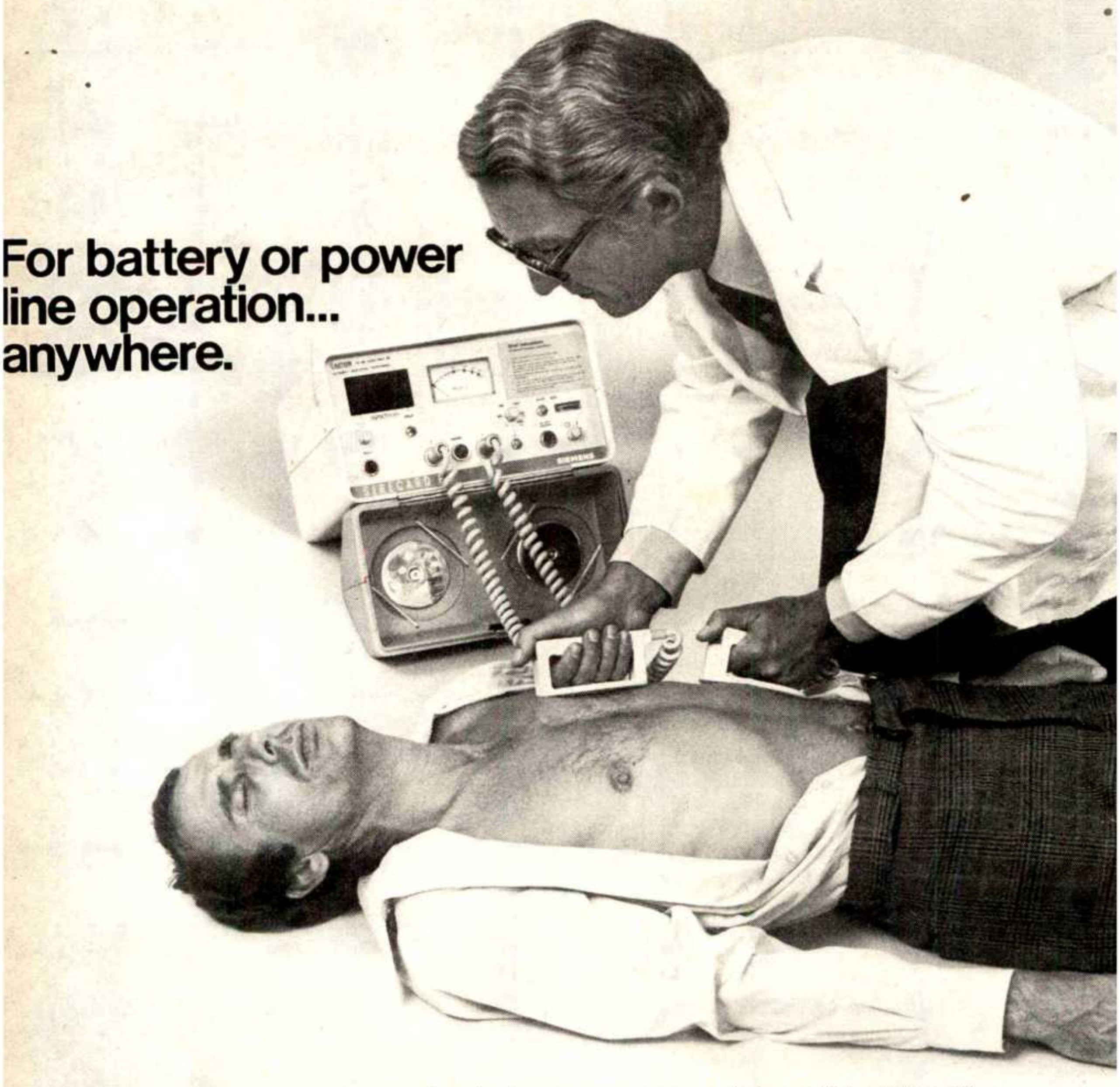

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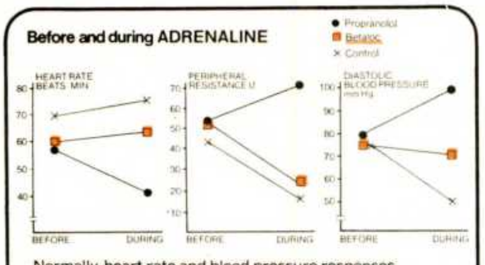

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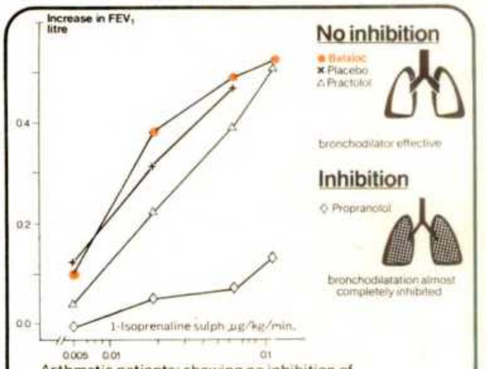

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1 (1975) *Acta pharmacol et toxi* Suppl. V, 39-68 University of Gothenburg, Sweden.

2 Clinical Report (1975), University of Gothenburg, Sweden.

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1. Lancet, 1973, ii, 399 2. Lancet, 1973, ii, 404 3. Amer. Heart J., 1976, *91*, 58
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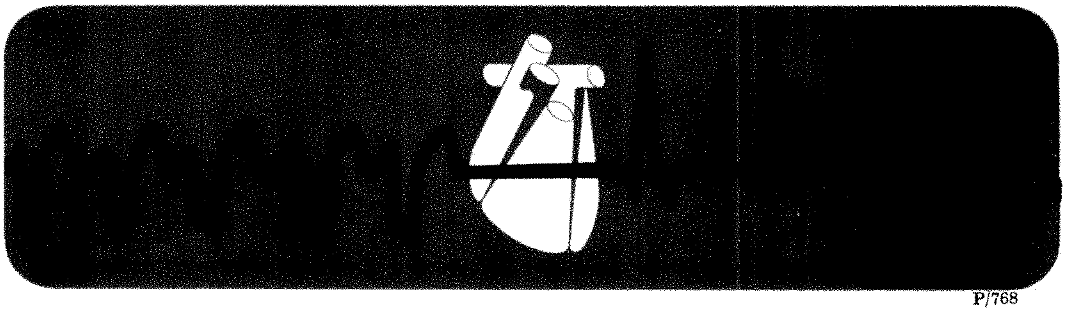

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Editorial

British Heart Journal, 1977, 39, 233–237

Eosinophilia and heart disease

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A wealth of literature testifies to the existence of an association between blood eosinoyhilia and cardiac disorder. Ever since Löffler described his two cases of 'endocarditis parietalis fibroplastica' with blood eosinophilia in 1936, this rare and dramatic clinical syndrome has excited attention (Brink and Weber, 1963; Jennings and Pengelly, 1968; Nagy *et al.*, 1969; Cline, 1969; Gardner-Thorpe *et al.*, 1971; Raizner *et al.*, 1972; Rasche *et al.*, 1973; Blair *et al.*, 1974; Bell *et al.*, 1976). Löffler's eponym is much used, especially when the eosinophilia is prominent and its cause obscure but other names abound to describe both overtly similar and seemingly adjacent disorders (Smith and Furth, 1943; Ware and Chapman, 1947; Becker *et al.*, 1953; Engfeldt and Zetterström, 1956; Odeberg, 1965)—*are they really different or are they merely variants of the same basic disorder?*

Pathological observations of the hearts of patients with prolonged eosinophilia have shown that both ventricles may be affected by a thrombotic endocarditis associated with eosinophilic infiltration, vasculitis, and myocardial necrosis (Brockington and Olsen, 1972; Olsen, 1975). Death may occur at this stage but more prolonged survival is followed by fibrous scarring and thickening of the endocardium, including the atrioventricular valves, and fibrous replacement of the inner myocardium. In severe cases organising mural thrombi may fill most of the cavities of the ventricles and embolism is common (Davies, 1960). The cardiac involvement may be associated with generalised eosinophilic infiltration involving other major organs (Hardy and Anderson, 1968; Shepherd *et al.*, 1971; Zucker-Franklin, 1971). Some of these cases have had a pseudo-leukaemia without abnormal myelopoiesis (Bousser, 1957) and others a genuine leukaemia, either eosinophilic or associated with eosinophilia (Bentley *et al.*, 1961; Yam *et al.*, 1972; Blatt *et al.*, 1974). Cardiac disorders may also develop with eosinophilia in status asthmaticus (Lennox, 1948), polyarteritis nodosa (Goodwin and Oakley, 1969), sensitivity to antituberculous drugs (Gardiol and Picht, 1957), and tropical eosinophilia associated with chronic infestations including filariasis (Vakil, 1961; Johny and Ananthachari, 1965). Chusid and colleagues (1975) found that at least 95 per cent of patients with a hypereosinophilic syndrome recorded in the published reports had clinical or necropsy evidence of myocardial disease.

Tropical endomyocardial fibrosis was first described from Uganda by Davies in 1948 after a clinical report by Bedford and Konstam (1946), and numerous further reports soon followed both from Davies and others in Uganda (Ball *et al.*, 1954; Davies, 1960) and also from West Africa (Abrahams, 1962). The characteristic sites of the endomyocardial lesions were well emphasised in these early studies. In the left ventricle the lesion, which is a scar, is strictly confined to the inflow tract. It may run from the posterior mitral leaflet to the apex where it ends abruptly in a distinctive ridge a short way up the septal wall (Davies, 1968) so sparing the anterior mitral leaflet, vestibule, and aortic valve entirely. The damage is often less extensive than this and may pick out either the apex or the region of the posterior leaflet. On the right side the process may be more massive and obliterate most of the right ventricle, but it still usually spares the infundibulum and pulmonary valve. The peculiar limitation of the left ventricular lesion may reflect the sites of maximum vortex impact on the walls of the filling ventricle (Bellhouse and Bellhouse, 1969) and suggests that the damaging agent is carried in the blood stream. The earliest manifestations of the pathological process within the heart are not well known. In Ibadan, Parry and Abrahams (1965) stressed the general constitutional illness which seemed to initiate the clinical cardiac disorder, and in the early fatal cases they found a freshly fibrosing endocardium, active fibroblasts, engorged smal blood vessels, and chronic inflammatory cells in the myocardium with areas of myofibre necrosis. Eosinophils were not mentioned but, as they noted in their paper, this initial illness had been spoken of also by French, Belgian, and Nigerian workers who had observed similar types of heart disease in West Africa and the Congo, which they had referred to as Löffler's disease or identified as a filarial cardiomyopathy. These patients had had an eosinophilia at some stage. While in tropical Africa an early constitutional illness with fever had been prominent in the Englishman with typical endomyocardial fibrosis reported by Brockington *et al.* in 1967.

In 1967, Ive *et al.* linked the geographical incidence of endomyocardial fibrosis in Nigeria with filariasis (and consequent eosinophilia) in an epidemiological study which showed that most patients came from forest areas where filariasis was common, and fell ill during the rainy season. Though their survey showed these similarities it failed to establish a cause and effect relation in Nigeria, and in Uganda the theory failed because in Uganda filariasis and endomyocardial fibrosis were not regionally associated at all.

The idea that a cardiac eosinophilia might have a pathogenetic role in African endomyocardial fibrosis came with the publication by Roberts of two cases of 'eosinophilic leukaemia' with mural endocardial sclerosis and superimposed thrombus, thrombotic valvular endocarditis, myocardial scarring, and generalised organ involvement. They predicated a spectrum of disease running from tropical eosinophilia to Löffler's disease with survival to develop Ugandan-type endomyocardial fibrosis as the end result of the endomyocardial eosinophilia (Roberts *et al.*, 1969, 1970). The next year, Brockington and associates (1970) described a further case of 'eosinophilic leukaemia' with endomyocardial fibrosis and thrombosis of the left ventricle. They considered that the cardiac lesion might have matured to typical endomyocardial fibrosis had the patient survived longer. Subsequently, fully developed typical endomyocardial fibrosis either with coexisting eosinophilia or in its absence has been described both from the U.S.A. (Libanoff and McMahon, 1976) and from this country (Faruque, 1963; Chew *et al.*, 1977). In this issue the Ugandan school report that their patients with established endomyocardial fibrosis have not shown abnormally high eosinophil counts but this observation surely cannot help elucidate whether or not the cardiac damage had been associated with an eosinophilia at its onset (Patel *et al.*, 1977).

In 1973, Brockington and Olsen compared 30 cases of Löffler's endocarditis with 6 non-trc cases without eosinophilia and 26 cases of myocardial fibrosis from Nigeria, Uganda, B and Europe. They showed that the fibrous sta Löffler's disease and endomyocardial fibrosis indistinguishable on histological grounds.

In South Africa, Becker and his colle (1953) recognised that a similar clinicopatholc picture to Löffler's disease could exist in the ab of eosinophilia and that if this feature wer garded as a variable phenomenon then many c cases published under a variety of terms mig belong in the same category.

As would be necessary for a unitarian th endomyocardial fibrosis is now being recognis Europeans who have never visited the trc Eosinophilia may be transient in Löffler's di (Weiss-Carmine, 1957) and is inconstant in Af patients with developed endomyocardial fib Since infestation with eosinophilia is much moner in Africans than in Europeans this account for the apparent differences in incic between endomyocardial fibrosis, a rare disorc the tropics, and Löffler's disease, an exceed rare disorder in Europe. Important circumst evidence is provided by non-tropical patients as Libanoff and McMahon's and Chew *et al.*'s who had both typical endomyocardial fibrosi persisting eosinophilia.

Loffler's disease with eosinophilia may pr with a grave constitutional illness and ofte severe right-sided failure conceals the signs o sided involvement until embolism occurs. If strictive pericarditis is suspected the presence murmur of mitral regurgitation (which is early to mid-systolic rather than pansys should betray the endocardial site of the disc Apical systolic murmurs were present in 20 cases reviewed by Brink and Weber (1963).

The unitarian theory remains unproven endomyocardial fibrosis the scarring is us limited to the left ventricular inflow tract wh many cases of Löffler's disease, the whole c may be involved and there may be a valvulitis vegetations. But if endomyocardial fibrosis r sents a milder form of Löffler's disease becau has permitted survival to the stage of sca surely a more restricted lesion is not unexpe Another difficulty which was re-emphasised rec by Bell *et al.* (1976) is the generalised arteritis v effects many organs in Loffler's disease while myocardial fibrosis primarily affects the heart since the eosinophilia may no longer persist a stage of endomyocardial fibrosis, the general ar may disappear too if they had, as we suppose, connected. A generalised arteritis may indeed have existed in the milder forms recognised by Hardy and Anderson (1968) and only those are likely to live to become chronic survivors. A further point in favour of the unitarian view is the high incidence of intracardiac thrombosis and embolism both in Löffler's disease with eosinophilia and in the disease which Becker described without eosinophilia. While embolism does occur in endomyocardial fibrosis (Shaper and Wright, 1963; Owor, 1973) it is fairly rare perhaps because the earlier stages of the disease are not recognised (Patel *et al.*, 1977). The apparent difference may be related to the lesser aggressiveness and greater chronicity of the process at the stage of endomyocardial fibrosis. Against the unitarian view, on the other hand, it is possible, or indeed likely, that endomyocardial fibrosis represents an end stage of any process which damages the endomyocardium, and that the eosinophil is only one of these. Carcinoid heart disease and methysergide heart disease also attack the endocardium, though neither are identical with endomyocardial fibrosis. A recent case report described endomyocardial fibrosis in a 21-year-old with acute myeloblastic leukaemia unassociated with eosinophilia but treated with daunorubicin (Wilcox *et al.*, 1976), a well-established cardiotoxic agent.

The clinical presentations of endomyocardial fibrosis are well known as a result of the comprehensive descriptions from Uganda (Shillingford and Somers, 1961; Connor *et al.*, 1967) and from Nigeria (Parry and Abrahams, 1963). The features vary greatly with the sites of the intracardiac lesions. Chronic right-sided disease may obliterate the cavity of the right ventricle almost completely without killing the patient who classically presents with proptosis and tense ascites. The condition may mimic constrictive pericarditis (Somers *et al.*, 1968) or present with pericardial effusion. Left-sided disease may simulate other cardiomyopathies and present with heart failure (Falase *et al.*, 1976). Tricuspid and/or mitral regurgitation (Clark *et al.*, 1956; Fowler and Somers, 1968) may be dominant and scar excision with valve replacement has recently been employed successfully (Cachera *et al.*, 1976). Rarely, the condition simulates primary pulmonary hypertension (Davies *et al.*, 1965) or an intracardiac tumour (Van der Hauwaert *et al.*, 1965). Clubbing and cyanosis are common with severe right-sided disease and secondary infective endocarditis is not unknown on the mitral valve (Falase *et al.*, 1976).

The main haemodynamic effect of the cardiac disorder (with or without persisting eosinophilia) is to restrict the filling and output of the ventricles, but the effect of this restriction is only felt in advanced cases and asymptomatic milder cases who do not seek treatment would evade recognition in societies whose patients are medically less sophisticated than our own. This could, perhaps, explain the absence of descriptions of mild endomyocardial fibrosis from those centres in tropical Africa from which the 'classical' forms were described and the late appearance of endomyocardial fibrosis in temperate climes where severe forms of the disorder are rare.

The European patients with endomyocardial fibrosis have started to emerge *pari passu* with the more thorough diagnostic investigations of asymptomatic patients which are now usual. The name 'primary restrictive cardiomyopathy' was recently coined to describe British patients believed to have a mild burned out form of Löffler's disease (Oakley, 1974), but, in such cases, proof of this is dependent on cardiac biopsy or accidental death from some non-cardiac cause.

The balance of the argument suggests that endomyocardial fibrosis represents both a later evolutionary phase and a milder burned out form of the disease which Löffler described. It is probable that the eosinophil is usually though not invariably involved; the underlying pathological processes are still unknown and further study and analysis of these conditions remain to be done.

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Endomyocardial fibrosis and eosinophilia

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Absolute eosinophil counts were assessed in 15 African patients with proven endomyocardial fibrosis. Though the mean eosinophil count in patients with endomyocardial fibrosis was higher compared with the normals reported from Kampala (1·13 vs 0·72×10⁹/1), the absolute range was comparable. A high percentage of patients with endomyocardial fibrosis had malarial parasites, high malarial antibody titres, hookworms, or strongyloides, but the correlation of eosinophilia to various parasitic infections was poor. Both eosinophilia and parasitic infections are common in the tropics and they affect patients with endomyocardial fibrosis no more than the population at large. Other aetiological factors, genetic, environmental, and immunological, are felt to be important in the causation of endomyocardial fibrosis in Uganda and evidence for this is reviewed. Though there is a similarity in pathological features, African endomyocardial fibrosis is a distinct entity from Löffler's endocarditis and cardiac lesions seen in eosinophilic leukaemia or reactive eosinophilia. There is no hard evidence to suggest that African endomyocardial fibrosis is a variant of Löffler's endocarditis caused by parasitic infections via eosinophilia.

Considerable knowledge of endomyocardial fibrosis has accumulated since its recognition as a clinicopathological entity by Davies and his co-workers (Ball *et al.*, 1954). While the clinical and haemodynamic features have been well delineated over the past decade (Somers *et al.* 1968a, b; and Connor *et al.* 1967, 1968), the cause of endomyocardial fibrosis remains unknown. Gerbaux and associates (1956) suggested that endocardial fibrosis and Löffler's endocarditis were essentially the same disease. Subsequently Roberts and associates (1969) reported 3 cases of 'eosinophilic leukaemia', without abnormal myelopoiesis but with endomyocardial lesions. They suggested that endomyocardial lesions in 'eosinophilic leukaemia', Löffler's endocarditis, and the endomyocardial fibrosis seen in Africa were the same disease. They further postulated that endomyocardial fibrosis without eosinophilia may be a later or inactive stage of either Löffler's endocarditis or 'eosinophilic leukaemia'. Brockington and Olsen (1973) reviewed 90 cases of cardiac lesions associated with eosinophilia, comparing them with 32 other fibrotic lesions including endomyocardial fibrosis from Uganda, Nigeria, and Brazil. Their conclusion was, 'There are no hard data to contradict the simple hypothesis that Davies' endomyocardial fibrosis is a late form of Löffler's endocarditis due to parasitic infections via eosinophilia'. Meanwhile, Bell *et al.* (1976) have shown that both the haemodynamic and angiographic findings in Löffler's endocarditis can mimic those described in endomyocardial fibrosis (Somers *et al.*, 1968a). Though eosinophilia has been implicated as an important link between Löffler's endocarditis and Davies' endomyocardial fibrosis, no detailed studies on eosinophilia have been reported from Uganda, which is the major focus besides Nigeria and Brazil. The present study was undertaken to: (1) assess absolute eosinophil counts in patients with endomyocardial fibrosis: (2) compare the eosinophil counts with those in normal individuals from the same area: (3) correlate the eosinophil counts to parasitic infections in these patients; and (4) differentiate features typical of African endomyocardial fibrosis from those of Löffler's endocarditis.

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Methods

Fifteen black African patients with endomyocardial fibrosis proven by cardiac catheterisation and cineangiography were studied. They were either inpatients or were attending the cardiology outpatient clinic at Mulago Hospital, Kampala. There were 10 male and 5 female patients, with ages ranging from 7 to 28 years. There were 10 Rwandans, i.e. they had originated from Rwanda or Burundi; 3 Ganda, i.e. indigenous to the Kampala region; and 2 from other tribes (Table 1). The white blood cell count was done according to the method of Dacie and Lewis (1963). The differential counts were all performed, on 200 cells, by a haematologist. A thick blood smear was examined for malarial parasites and microfilaria. Malarial antibody tires were estimated by the fluorescent antibody technique of Voller and Bray (1962) using human films containing *Plasmodium falciparum*. Stool examination was performed by the formol-ether concentration method followed by direct examination under the microscope (King, 1966).

Table 1 *Sex, age, ethnic group, and liver biopsy results in patients with endomyocardial fibrosis*

Case No.	*Sex*	*Age*	*Ethnic group*	*Liver biopsy*
1	M	18	Hangaza	0
2	M	26	Ganda	Normal
3	M	15	Ankole	TSS
4	F	7	Rwanda	Congested
5	M	15	Rwanda	Normal
6	M	28	Rwanda	Congested
7	F	26	Rwanda	Cirrhosis
8	F	16	Rwanda	TSS
9	M	9	Rwanda	TSS
10	F	28	Rwanda	Normal
11	M	20	Ganda	Congested
12	M	17	Rwanda	Normal
13	M	17	Rwanda	Congested
14	F	13	Ganda	Cirrhosis
15	M	10	Rwanda	0

0, not done; TSS, tropical splenomegaly syndrome.

Table 2 *White blood cell, neutrophil, and eosinophil counts in patients with endomyocardial fibrosis*

Case No.	*Hb g/l*	*WBC* $\times 10^9$*/l Total*	*Neutrophils*		*Eosinophils*		*Others*	
			%	*Absolute*	*%*	*Absolute*	*%*	*Absolute*
1	134	5	23	1·15	52	2 60	25	1·25
2	158	4	37	1·48	35	1·40	28	1·12
3	130	5	53	2 65	9	0 45	38	1·90
4	120	10	45	4·50	13	1 30	42	4·20
5	122	4	16	0 64	31	1·24	53	2 12
6	100	8	60	4 80	4	0 32	36	2 88
7	112	7	37	2·59	24	1·68	39	2 73
8	130	5	28	1·40	33	1·65	39	1·95
9	112	4 5	27	1·22	15	0·68	58	2·61
10	128	6	42	2·52	30	1·80	28	1 68
11	122	3	62	1·86	11	0 33	27	0 81
12	152	3	61	1·83	11	0 33	28	0·84
13	70	4	44	1·76	1	0 04	55	2·20
14	128	5	13	0 65	30	1·50	57	2·85
15	93	5	24	1 20	31	1·65	45	2·25
Mean		5·23		2 01		1·13		
Range		3–10		0·64–4·80		0·04–2 60		
% mean			38		22			
Mean		5·10		1·96		0 72	Shaper (1972) (African, Kampala)	
Range		1 90–8 30		0·32–3·60		0–2·26		
% mean			39		12			
Mean		7·00		3·65		0 15	Wintrobe (1974)	
Range		4·30–10 00		1 83–2·25		0–0·70		
% mean			53		3 2			

These values are compared with the normals reported by Shaper in healthy African subjects from Kampala and Wintrobe from U.S.A. Shaper and Wintrobe figures give 95 per cent confidence limits: endomyocardial fibrosis figures give full range.

Results

WHITE BLOOD CELL COUNTS

Table 2 summarizes detailed white cell count in 15 patients with endomyocardial fibrosis. These values are compared with normals from the Kampala area (Shaper, 1972), and from values quoted by Wintrobe (1974). The total white blood cell and neutrophil counts were lower, and the eosinophil counts higher in both the normals and patients with endomyocardial fibrosis from Kampala, compared with values reported by Wintrobe. Though the average eosinophil percentage was higher in the patients with endomyocardial fibrosis, the absolute range was comparable.

MALARIAL PARASITES, MALARIAL ANTIBODY TITRES, MICROFILARIA, AND INTESTINAL PARASITES

Table 3 summarises various parasites found in patients with endomyocardial fibrosis. Three patients had malarial parasites in their blood stream, and 9 patients had malarial antibody titres of 1 in 800 or greater. Microfilaria *Dipetalonema perstans* was found in 4 patients. Various intestinal parasites were detected in 10 patients, the commonest one being hookworms and the species *Necator americanus.* The correlation between

Table 3 *Malarial parasites, malarial antibody titres, microfilaria, and stool parasites in patients with endomyocardial fibrosis*

Patient No.	*BS for MP*	*MABT*	*Microfilaria*	*Stool parasite*
1	0	1:1600	DP	HW, Tr
2	0	1: 100	0	0
3	+	1:1600	DP	HW
4	0	1: 200	0	HW
5	0	1: 800	0	HW
6	0	1: 200	0	HW
7	0	1:1600	0	HW
8	0	1: 100	0	0
9	+	1:1600	DP	0
10	0	1: 800	0	HW, St
11	0	1: 100	0	0
12	0	1: 200	DP	St
13	0	1:1600	0	HW
14	+	1:1600	0	0
15	0	1:1600	0	HW

BS, blood slide; MP, malarial parasites; MABT, malarial antibody titres; DP, *Dipetalonema perstans*; HW, hookworms; Tr, *trichuris;* St, *stronglyloides;* 0, none; +, positive.

eosinophilia and the presence of hookworm was poor. Of 9 patients with hookworm, 6 had an absolute eosinophil count over $0{\cdot}80\times10^9/1$, while 3 out of 6 patients without hookworm had an eosinophil count in the same range.

LIVER BIOPSY

Liver biopsies were done in 13 patients to assess tissue oesinophilia or changes consistent with tropical splenomegaly syndrome. Eight patients had normal liver architecture and/or changes secondary to liver congestion from heart failure. Two patients had cirrhosis. Three patients had sinusoidal infiltration with lymphocytes consistent with tropical splenomegaly syndrome attributed to chronic malarial infection (Hutt and Hamilton, 1972).

Discussion

Indigenous African people have a white blood cell count pattern which differs from that usually described in the standard textbooks of haematology. The total leucocyte counts and neutrophils are lower than in Caucasians and the eosinophil counts are higher. Any haematological study in Africans must be compared with normals from that particular area. The total white cell count and neutrophil counts in the patients with endomyocardial fibrosis are comparable to the values reported from 250 normal individuals from the Kampala area by Shaper (1972). Of the normal Africans, 49 per cent showed an eosinophilia of $0{\cdot}50\times10^9/1$, 18 per cent were over $1{\cdot}00\times10^9/1$, and 5 per cent were over $2{\cdot}00\times10^9/1$. The majority (39%) of normal Africans showing an eosinophilia were Rwandans. Though the average eosinophil percentage was higher in the patients with endomyocardial fibrosis, in the present study the absolute range was comparable to the normal Africans. A high eosinophil count is common in the tropics, and though various intestinal and blood parasites have been incriminated as a cause, its genesis remains unexplained. Intestinal parasitism is less regularly associated with eosinophilia than is parasitism in which tissue invasion is prominent. A high incidence of hookworms was found in patients with endomyocardial fibrosis, but the relation between eosinophilia and the presence of hookworms was poor. In another study reported from the tropics, no correlation was observed between the oesinophil levels and parasitic infection (Ashcroft *et al.*, 1969).

Ive and associates (1967) found evidence of exposure to one or the other form of filariasis in patients with endomyocardial fibrosis from West Africa. In Kampala most of the patients with endomyocardial fibrosis come from areas free of onchocerciasis (Shaper and Coles, 1966). None of the 15 patients in the study had any past history or clinical features consistent with onchocerciasis. *Dipetalonema perstans* is a common non-pathogenetic filariasis found in up to 50 per cent of blood donors in the Kampala area (Shaper, 1972). A high frequency of heart antibodies and autoimmunity against the heart in endomyocardial fibrosis has been shown by van der Geld and his Ugandan associates (1966). Shaper *et al.* (1968) described an immunological syndrome in Rwandans characterised by high titres of malarial antibody and a high incidence of heart, thyroid, and parietal cell antibodies. While this syndrome affects predominantly the people originating from Rwanda and Burundi, areas relatively free of malaria, it does affect the Ganda people indigenous to the highly malarious area. Nine patients in this study had evidence of malaria either on direct blood smear or by high malarial antibody titres. Three patients had histological changes of tropical splenomegaly syndrome. It is probable that the presence of tissue antibodies associated with an unusual host response to malarial infection may play a critical role in the pathogenesis of endomyocardial fibrosis (Patel *et al.*, 1971).

The degree of eosinophilia varies considerably among patients with Löffler's endocarditis, eosinophilic leukaemia, or reactive eosinophilia, and endomyocardial fibrosis. Counts of 2 to $5\times10^9/1$ are not unusual in the former entities. The absolute eosinophil count in patients with endomyocardial fibrosis has been relatively low. Though it has been postulated that eosinophilia may be intense only in the acute stage (Roberts *et al.*, 1969), from observations by cardiologists and pathologists in Kampala, where endomyocardial fibrosis accounts for 12 per cent of all heart disease (Somers *et al.*, 1972), no such progression has been observed. At necropsy, where acute cases are recognised by endocardial lesions with a spongy, grey-green layer of thrombus, detailed histopathological studies by Connor and associates (1967, 1968) failed to show tissue eosinophilia in early or well-established lesions. Among the few patients in the present study who had endomyocardial biopsies in life (Somers *et al.*, 1971), or who came to necropsy, none showed tissue eosinophilia. Liver biopsies also failed to reveal any tissue eosinophilia.

There are important differences in the clinical presentation of endomyocardial fibrosis seen in the tropics and Löffler's endocarditis. The former is a disease of children and young adults. In Uganda there is a striking predilection for the immigrants from Rwanda and Burundi. The natural history of the disease has been difficult to study, since the earlier stages of the disease are not recognised. The disease is only recognised when the haemodynamic disturbance secondary to endocardial restriction and valvular regurgitation produces overt symptoms. Pericardial effusion with a high protein content but low cell count is common on first presentation, disappears during the follow-up, and recurs again terminally. Embolic manifestations may be present in 16 per cent of the patients. They involve the large arteries, often occluding the aorta completely. This clinical presentation is in sharp contrast to Löffler's endocarditis and endomyocardial involvement in eosinophilic leukaemia or reactive eosinophilia. The evidence linking eosinophilia and parasitic infections to endomyocardial fibrosis cases seen in Uganda is lacking. Both eosinophilia and parasitic infections are common in the tropics, but they affect patients with endomyocardial fibrosis no more than the population at large. Other aetiological factors, genetic (Patel *et al.*, 1971), and/or environmental and immunological, may be much more important in the causation of endomyocardial fibrosis in Uganda. Bell and his associates (1976) have suggested that the similarity of the pathogenetic mechanisms in Löffler's endocarditis and endomyocardial fibrosis perhaps reflects a restricted spectrum of endocardial response to disease. While not in dispute with this hypothesis, we are in agreement that there is no basis for regarding Löffler's endocarditis and endomyocardial fibrosis as variants of a single entity.

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A study of systolic time intervals during uninterrupted exercise[1]

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A method has been developed for obtaining measurements of the systolic time intervals during uninterrupted graded exercise in the upright position on a bicycle ergometer.

The method has been applied to 112 subjects divided into 4 groups: two of normal subjects below and above the age of 40, respectively (mean ages 30 and 48 years), and two of patients (mean ages for each about 50 years), both with coronary insufficiency, but one without and the other with abnormality of left ventricular function as shown by ventriculography. The measurements obtained yield linear relations between total electromechanical systole (QS_2) and heart rate, between pre-ejection period (PEP) and RR interval for each subject. The average standard deviation about the regression is less than 6 ms for all three regression lines; the average correlation coefficient is greater than 0·93.

The younger group of normal subjects have a significantly shorter PEP compared to the older group. Indices have been derived which separate the patient groups from each other and from the normal subjects. Using these indices 86 per cent of all the subjects were correctly classified according to the group to which they belonged. It is concluded that measurements of STI during uninterrupted exercise offer valuable information in the assessment of cardiac patients.

Non-invasive techniques have become increasingly important in the evaluation of cardiovascular dynamics and myocardial performance in man. The clinical application of systolic time intervals (STI) has recently received more attention (Weissler, *et al.,* 1972). It has been shown that there are differences in STI between normal subjects and patients with cardiac disorders (Toutouzas *et al.,* 1969; Samson, 1970; Sultan Ahmed *et al.,* 1972; Fabian *et al.,* 1972b; Johnson *et al.,* 1972; Armstrong *et al.,* 1973; De Monchy *et al.,* 1973; Beneken *et al.,* 1974). For recent reviews of STI see Wayne (1973) and Harris (1974). For detection of coronary artery disease the results have been disappointing because of statistical overlap with normal subjects (Weissler *et al.,* 1969; Aronow *et al.,* 1971; Buyukozturk *et al.,* 1971; Whitsett and Naughton, 1971; Clerens *et al.,* 1973). Several studies, however, have shown the left ventricular ejection time to be a useful index of cardiac function (Schoenfeld *et al.,* 1967; Wayne, 1968; Diamant and Killip, 1970; Inoue *et al.,* 1970; Heikkilä *et al.,* 1971; Hamosh *et al.,* 1972). At rest, the systolic ratios seem to be the best single index of ventricular function, correlating well with reduced ejection fraction (Meng *et al.,* 1975). The best results have been reported with the ratio ejection time/isovolumetric contraction time; the ratio ejection time/pre-ejection time was considered inferior (Pouget *et al.,* 1971; McDonald and Hobson, 1974).

Systolic time intervals can be obtained at rest, during or after exercise in the supine, sitting, or standing position. Weissler (1972) and McConahay (1972) pointed out that for exercising normal subjects regression equations should preferably be developed, because the relations between intervals and heart rate found during exercise differ widely from those established at rest for the same subjects. 'Correcting for heart rate', using Weissler *et al.*'s (1969) regression formula, derived from subjects at rest, cannot be applied suitably to results obtained

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from measurements during exercise. This has been confirmed by us in an earlier study (Van der Hoeven *et al.*, 1973).

Exercise studies thus far have not improved the diagnostic value of systolic time intervals, which seems to be partly because measurements were made after interruption of upright exercise and changing to the recumbent position (Whitsett and Naughton, 1971; Pouget *et al.*, 1971) or by measuring intervals in the supine position after supine exercise (McConahay *et al.*, 1972). In an earlier study in which we tried to obtain objective evidence concerning the effect of coronary bypass surgery on left ventricular performance, we used an invasive technique to measure ejection times *during* exercise and found these to be rather long before bypass surgery and considerably shorter after surgery (Vonk *et al.*, 1971). We have now developed a technique for obtaining STI measurements during uninterrupted exercise in the sitting position on a bicycle ergometer and have derived individual values of the STI as a function of the heart rate, obtained from two groups of normal subjects and two groups of patients with coronary arterial disease.

This study was designed to answer the following two questions:

(a) What are the changes of STI of normal subjects and of patients with ischaemic heart disease when subjected to a standardised exercise test?

(b) What are the differences in response for the different groups of healthy subjects and patients, and is it possible to find a set of values on the basis of the exercise STI by which an individual subject may be identified as a member of one or the other groups?

Subjects

Measurements were performed on two groups of normal adults (N) and two groups of patients (P).

(1) 18 young subjects ($N_{<40}$) between 21 and 38 years old (mean 29·5 years).

(2) 33 older subjects ($N_{>40}$) between 41 and 66 years old (mean 48·0 years). Both groups of normal subjects consisted of healthy laboratory workers, hospital personnel or subjects referred to outpatient departments for cardiac examination. These subjects received a complete physical examination, including 12-lead electrocardiogram, exercise test, chest *x*-ray, and serum lipid level determination No evidence of cardiovascular disorder was found. All normal subjects were asymptomatic and none took any form of medication. (There was one woman in each group.)

(3) 36 patients (P_1) between 36 and 63 years old (mean 50·4 years). Patients with classical angina pectoris, subjected to coronary arteriography and left ventriculography with one-, two-, or three-vessel disease with stenosis >75 per cent but with a normal ventriculogram.

Table 1 *Subdivision of patient groups according to criteria of the New York Heart Association*

Patient group	*Total No.*	*Class*			
		I	*II*	*III*	*IV*
P_1	36	8	24	4	0
P_2	25	3	14	8	0

Abbreviations see Table 2.

(4) 25 patients (P_2) between 34 and 57 years old (mean 48·6 years). As group P_1 but with an abnormal ventriculogram showing local hypokinesia, akinesia, or dyskinesia.

The severity of the anginal complaints in the two groups of patients can be seen in Table 1 where the functional class according to the criteria of the New York Heart Association is given. The exercise tolerance of the subjects in the four groups is given in Table 2. The normal subjects were divided into two subgroups to provide a group of older normal subjects, with an age distribution comparable to that of the patient groups. The exercise tolerance of the $N_{>40}$ group is more comparable to the patient groups as shown in Table 2.

Methods

EXERCISE PROCEDURE

To obtain the systolic time intervals during exercise, the subjects pedalled on either a Muller[1] or a Lode[2] bicycle ergometer. The load on both bicycles was continuously adjustable. The procedure was started

Table 2 *Exercise tolerance of subjects in all classes*

Group	*Total No.*	*No. of subjects reaching maximal load of (Watts)* *<70*	*70–90*	*100–120*	*130–150*	*>150*
$N_{<40}$	18	0	0	1	3	14
$N_{>40}$	33	0	6	13	14	0
P_1	36	3	13	16	3	1
P_2	25	1	10	12	2	0

$N_{<40}$ normal subjects, age less than 40; $N_{>40}$ normal subjects, age over 40; P_1 cardiac patients with coronary insufficiency but normal ventriculogram; P_2 cardiac patients with coronary insufficiency and abnormal ventricular contraction pattern.

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[1] Zentrallwerkstatt GmbH, Göttingen, Germany; Type Nr. 67009.

[2] Lode's Instrumenten N.V., Groningen, The Netherlands; Type 'Lanooy'.

at zero load with a pedal rate of 60 revolutions per minute; this rate was held constant throughout the test. After 1 minute the load was increased 10 Watts each minute. The condition of the subject (fatigue, dyspnoea) or changes in the electrocardiogram (ST depression or ventricular premature beats) determined the termination of the exercise.

MEASURING TECHNIQUE

The carotid pulse wave (CPW), the phonocardiogram (PCG), and a single lead electrocardiogram (ECG) were recorded on a Hellige multichannel strip chart recorder Type 9400 or 9900/4, at a paper speed of 100 mm/s. To record the carotid pulse wave during exercise, we used the specially developed transducer, described by Van der Hoeven and Beneken (1970). Our transducer senses the carotid arterial vessel wall displacement by a feeler pin, which is attached to a leaf spring. A semiconductor strain-gauge is fixed to this leaf spring. This transducer has been tested in dog experiments and the signal produced shown to represent very accurately the time course of the intravascular pressure wave.

The transducer was attached to the subject's neck above the right carotid artery, using a foam-padded aluminium strip and a rubber band. The subject was asked to stretch his neck region by keeping his chin slightly raised and turned to the left, while he watched a dial that indicated his cycling rate. In this manner, it was possible to obtain carotid pulse waves during pedalling at different load levels, without having to interrupt the procedure temporarily to take the measurements. In an earlier study the reliability of the external determination of the left ventricular ejection time (LVET) obtained from the carotid pulse wave was tested (Van der Hoeven *et al.*, 1973). Comparison of internally and externally measured LVET values showed that the accuracy was well within the range needed for this study. The resulting regression equation was:

LVET (external)$=0{\cdot}98$ LVET (intra-arterial) $+3$ ms; correlation coefficient$=0{\cdot}99$; standard deviation about regression$=1{\cdot}5$ ms.

The phonocardiogram was obtained from an acceleration microphone[3] applied to the left third intercostal space at the position where the aortic component of the second heart sound appeared maximally. The microphone was fixed in position with double-sided adhesive tape and, in order to secure good contact with the chest wall, a 3 cm wide rubber band was wrapped around the microphone and chest. This did not interfere with the subject's respiration. The signal was filtered using the high-pass Maass-Weber (1952) phonofilter Mm 1, with a slope of −24 db/oct (the −20 db point at 70 cps).

The electrocardiogram was recorded using disturbance-free skin electrodes[4], consisting of silver cups, filled with conducting jelly, in a rigid housing. Linen gauze was attached to the housing and glued to the skin (Boter *et al.*, 1966). A good Q wave without artefacts from muscle activity was obtained with the CM5 lead (electrodes in position V5 and on the manubrium). To eliminate any electrical shock hazard, either the electrocardiogram was telemetered via a battery-powered transmitter, or the leads were insulated by an isolation amplifier. Systolic blood pressures were measured with a normal arm cuff; pressures were measured only for monitoring and not recorded.

DEFINITIONS OF SYSTOLIC TIME INTERVALS

Fig. 1 shows the definitions of the systolic time intervals: total electromechanical systole (QS_2); left ventricular ejection time (LVET); pre-ejection period (PEP).

The definitions follow the description as given by Weissler *et al.* (1969). Fig. 2 illustrates the electrocardiogram, phonocardiogram, and the carotid artery pulsation signal at increasing load levels, obtained from a normal subject during uninterrupted exercise on the bicycle ergometer. Normally, the data points were obtained from the recording, during the final 10 seconds of each minute, just before the next load step except that below 20 Watts, at the beginning of the test, no measurements were made because of the effects of the transition between rest and exercise. The number of data points available for calculating the regression lines for each subject varied for the following reasons:

(1) The duration of the test varied according to the maximal exercise tolerance of the subject.

(2) In about 5% of cases it was not possible to assess all sections of the recordings, because of bad quality.

The average number of data points available for the normal groups was 11 (SD$=2{\cdot}1$) and $8{\cdot}8$ (SD$=2{\cdot}4$) for both patient groups.

PROCESSING OF INDIVIDUAL DATA

The processing of the STI, obtained during an exercise test, is illustrated by the results obtained on Subject 1 (normal group $N_{<40}$). The values of QS_2, LVET, the RR interval for each load, obtained for this subject are shown in Table 3A. Every value in this table is an average over at least five consecutive heart beats at the pertinent load level.

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[3] Type EMT 25B Elema-Schonander, Solna, Sweden.

[4] Dépex N.V., The Netherlands.

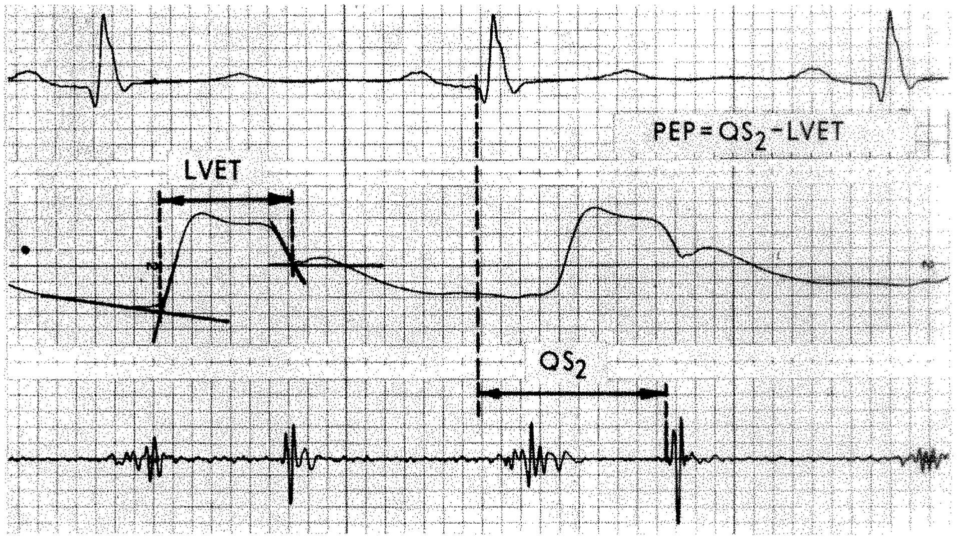

Fig. 1 *A sample of a continuous recording from which the systolic time intervals were measured. From top to bottom: electrocardiogram, external carotid artery pulse wave, and phonocardiogram. The tangents shown in the tracings indicate the procedure to determine beginning of upstroke and incisura.*

From previous studies (Van der Hoeven *et al.*, 1973) and from the analysis of the results of this study (see Discussion) it appears that there are linear relations between QS_2 versus HR, the LVET versus HR, and the PEP versus the RR interval. The individual regression lines calculated, using the method of least squares, from the data of Table 3A are given in Table 3B and Fig. 3.

Each of the three regression lines (QS_2 versus HR, LVET versus HR, PEP versus RR interval) may be described by the equation

$$y=mx+n$$

where m represents the inclination or slope of the line and n its intersection with the y-axis at $x=0$. To compare the regression lines of the individual subjects, the slopes (m) and the values of y at a standardised x value, close to the average heart rate, may be used. The average heart rates of the patients are usually lower compared with normals, because of the limited exercise tolerance of the patients. Therefore, we chose 2 standard values for the heart rate ($x=100$ and $x=130$ bpm) to calculate the corresponding ordinate values: $y_{(100)}=100m+n$ and $y_{(130)}=130m+n$. For the regression line PEP versus RR interval, a heart rate of 100 bpm corresponds to an RR interval of 600 ms and 130 bpm corresponds to 462 ms. So, $PEP_{(100)}$ is calculated by $PEP_{(100)}=600m+n$.

Further studies are required to determine which standardised heart rate provides the best values for a correct classification of patients and normals.

To describe the results we took three quantities into the analysis for each regression line: m, $y_{(100)}$, and $y_{(130)}$, which resulted in 9 values for each subject. These nine are not completely independent.

Results

Table 4 gives the mean and standard error of the mean for each set of values in each class. Averaging the individual regression coefficients results in an average regression equation for each systolic interval and for each group. These regression equations are presented in Table 5 and in graphical form in Fig. 4. The significant differences of the desired parameters compared with those of $N_{>40}$ as the control group are indicated in Table 4. In addition, the significant differences between the values for the P_1 and P_2 group are given. Even though there is a significant difference between the mean values of two sample distributions, it is often not possible to classify the individual members correctly because of a large overlap of the distributions. None of the parameters, as listed in Table 4, is adequate for the classification of normals and patients, the number of false positives and false negatives being too large. Therefore, we have to look for a combination, linear or non-linear, of the values, such that the resulting set of new values will

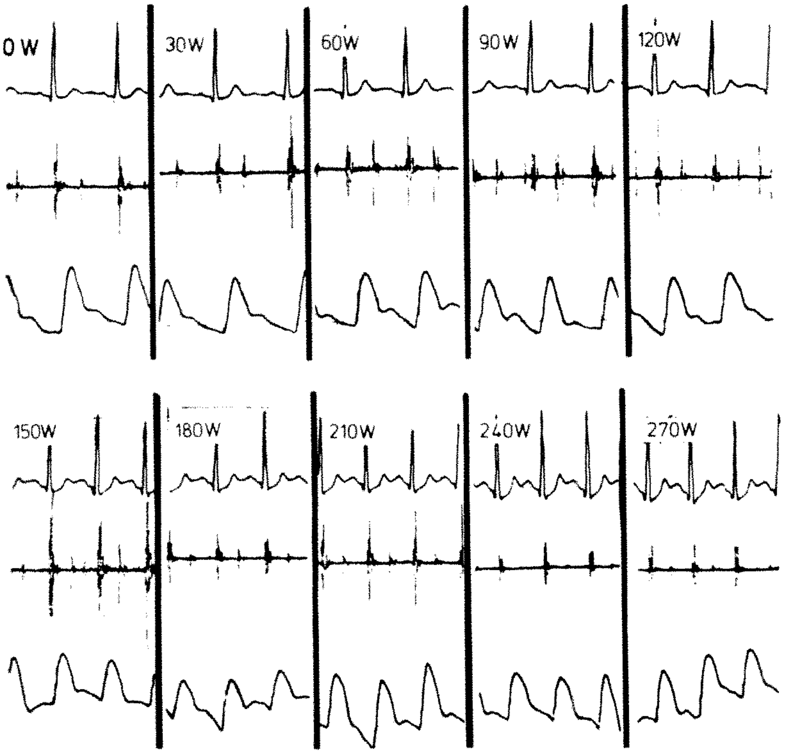

Fig. 2 *Samples of recordings at different loads obtained from a normal adult during uninterrupted exercise. The load, in Watts, at which the samples were taken is indicated.*

give a better separation between the clusters of normals and patients.

Analysing the individual values two indices were found, which are defined as follows:

$$\text{Index } 1 = \frac{QS_{2(130)} - 230}{-m_{LVET}} \quad \text{(bpm)}$$

$$\text{Index } 2 = \frac{PEP_{(100)}}{LVET_{(100)}}$$

The individual indices for each subject are plotted in Fig. 5. As shown in the figure, P_1 patients are characterised by a relatively high value of $QS_{2(130)} - 230/{-m_{LVET}}$ and P_2 patients are characterised by a high index $PEP_{(100)}/LVET_{(100)}$.

The average values and the SEM of the indices

Table 3A *Mean systolic time intervals at increasing load levels obtained from Subject 1 (group* $N_{<40}$*)*

Sample (No.)	*Load (Watt)*	*HR (bpm)*	*QS_2 (ms)*	*LVET (ms)*	*PEP (ms)*
1	20	79	376	272	104
2	30	85	370	272	98
3	40	83	369	272	97
4	50	84	375	275	100
5	70	84	355	268	87
6	80	97	351	260	91
7	90	94	354	271	83
8	100	100	335	256	79
9	120	108	322	254	68
10	130	113	312	244	68
11	140	115	310	244	66
12	150	117	306	244	62
13	170	131	289	226	63
14	190	136	276	225	51
15	210	145	267	215	52
16	230	153	257	215	52
17	250	160	254	206	48

Table 3B *Regression equations obtained from data in Table 3A*

Regression equation	s_m	s_{yx}	r
$QS_2 = 501 - 1{\cdot}61\ HR$	0·062	6·5	−0·99
$LVET = 346 - 0{\cdot}88\ HR$	0·033	3·4	−0·99
$PEP = -11 + 0{\cdot}15\ RR$	0·009	4·5	+0·97

HR, heart rate in bpm; RR, RR interval (ms); QS_2, electromechanical systole; LVET, left ventricular ejection time; PEP, pre-ejection period; s_m, standard error of the slope m; s_{yx}, standard error about regression; r, correlation coefficient.

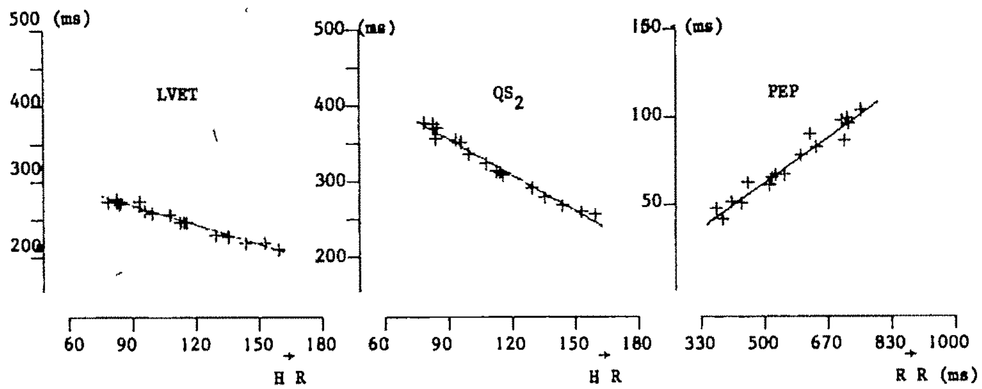

Fig. 3 *LVET versus HR, QS_2 versus HR, and PEP versus RR interval for one normal subject during uninterrupted exercise on a bicycle ergometer. Data points, indicated by crosses, are tabulated in Table 3. Observe the nice fit of the data points by a linear regression line.*

Table 4 *Ejection fraction, and 9 STI measurements obtained during exercise for each group (mean ± SEM)*

		Group				
		$N_{>40}$	$N_{<40}$	P_1	P_2	
No.		33	18	36	25	
Mean age (yr)		48	30	50	49	
Ejection fraction		—	—	0·62 ±0 02	0·45 ±0 02	(*)
$QS_{2(100)}$	(ms)	332 ±2 0	321 ±2·9*	347 ±2·9*	328 ±2 6	(*)
$QS_{2(130)}$	(ms)	282 ±2 4	277 ±2·6	303 ±3·1*	283 ±2·8	(*)
m_{QS_2}	(ms/bpm)	−1·68 ±0·04	−1·45 ±0 04*	−1·45 ±0 05*	−1 50 ±0 09**	
$LVET_{(100)}$	(ms)	241 ±1·6	238 ±2 9	249 ±2 2*	220 ±2 2*	(*)
$LVET_{(130)}$	(ms)	210 ±1 5	211 ±2·5	227 ±2·6*	194 ±2 2*	(*)
m_{LVET}	(ms/bpm)	−1 03 ±0·03	−0·91 ±0·03**	−0·71 ±0·05*	−0 86 ±0 06**	(**)
$PEP_{(100)}$	(ms)	91 ±1·3	82 ±2·2*	98 ±1·9*	108 ±2·5*	(*)
$PEP_{(130)}$	(ms)	72 ±1·2	65 ±1 7*	79 ±1·4*	90 ±3 1*	(*)
m_{PEP}		0 13 ±0·006	0·12 ±0·01	0·14 ±0 01	0·13 ±0 01	

*$P < 0\ 005$, **$P < 0·05$ with $N_{>40}$ as control group.
Between parentheses (last column) the significance of the differences between group P_1 and group P_2. Abbreviations as in Tables 2 and 3. Indices in first column indicate the heart rates (100 and 130 bpm) at which the STI are computed.

Table 5 *Mean regression equations for four groups*

Group	*Regression equation*	*R*	*S_{yx}*
$N_{>40}$	QS_2 = 500−1 68 HR	−0 98	6·0
$N_{<40}$	QS_2 = 466−1·45 HR	−0·98	5 6
P_1	QS_2 = 492−1·45 HR	−0·96	5·3
P_2	QS_2 = 478−1 50 HR	−0 96	5·2
$N_{>40}$	LVET = 344−1·03 HR	−0 98	3·5
$N_{<40}$	LVET = 329−0·91 HR	−0 96	5·6
P_1	LVET = 320−0 71 HR	−0·88	3 8
P_2	LVET = 306−0·86 HR	−0 95	3·6
$N_{>40}$	PEP = 13 + 0·13 RR	0·94	4·1
$N_{<40}$	PEP = 10 + 0·12 RR	0·94	4·5
P_1	PEP = 14 + 0·14 RR	0 94	3·9
P_2	PEP = 30 + 0·13 RR	0 85	3 5

R, mean correlation coefficient of the individual regression lines; S_{yx}, mean standard deviation about regression (ms). Other abbreviations as in Tables 2 and 3.

are indicated in the figure. A rationale for the choice of the two indices is presented in the discussion.

EJECTION FRACTIONS

All patients underwent cardiac catheterisation and from 29 P_1 and 22 P_2 patients the ejection fraction could be estimated reliably from the ventriculogram in the right oblique position, using the method of Sandler and Dodge (1968). Average values and SEM of the ejection fractions for the two patient groups are given in Table 4.

Discussion

SOURCES OF ERROR

The average regression coefficients as presented in Table 4 are known with a limited accuracy, partly

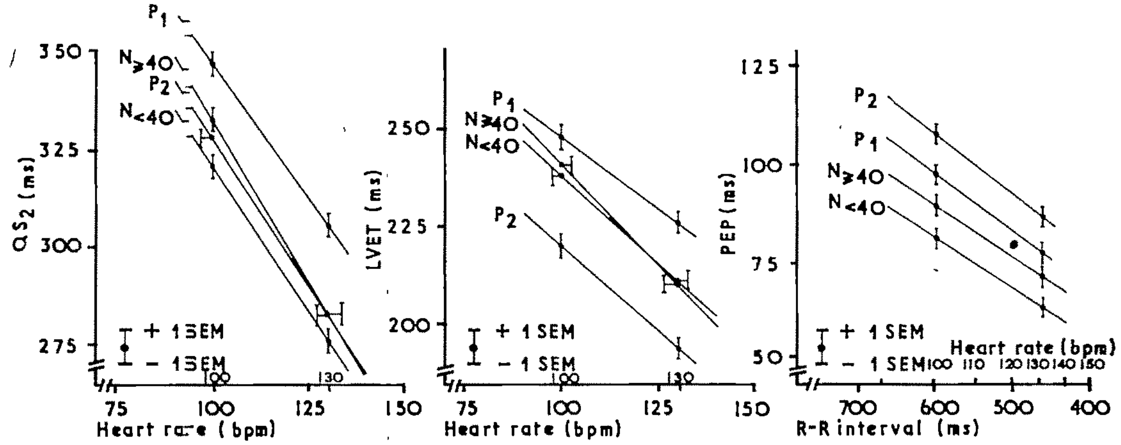

Fig. 4 Graphical representation of the relation between QS_2 and HR, LVET and HR, and PEP and RR interval, for the 4 groups of subjects. Lines are drawn as given by the data in Tables 4 and 5.

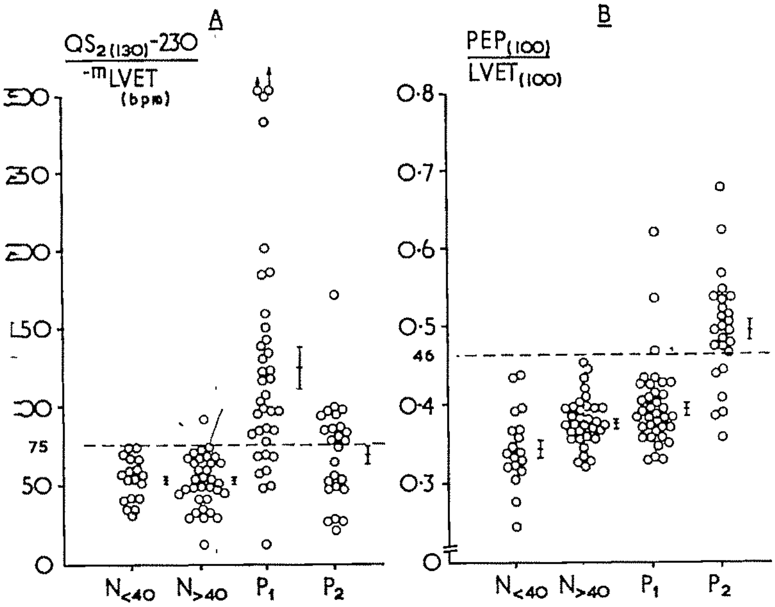

Fig. 5 *Panel A: Index* $1=(QS_{2(130)}-230)/-m_{LVET}$ *for all subjects in each group. Mean values ±1 SEM are indicated. Abbreviations as in Tables 2 and 3. A horizontal line at Index 1=75 separates* P_1 *subjects from normal subjects. One value (at Index 1=2300) for a* P_1 *subject is excluded from the computation of the mean and SEM. This value is extremely high because of an almost zero value of* m_{LVET}.
Panel B: Index $2=PEP_{100}/LVET_{100}$ *for all subjects in each group. A horizontal line at Index 2=0·46 separates* P_2 *subjects from normal subjects.*

expressed by their standard deviation. There are several possible sources of inaccuracy:

(a) Inaccuracy of individual data points: Our experience is that individual time intervals may be estimated within 3 ms of the true value, which is in accordance with the value given by Aronow *et al.* (1971). Since five or more beats were taken for the calculation of one data point, the inaccuracy of data points is of the order of 1 to 2 ms.

(b) The use of a linear model to fit the data points: We have used linear models for the relation between the systolic intervals and heart rate (or RR interval for the PEP). These models are validated by the individual values of the linear correlation coefficient, which is larger than 0·85 in 95 per cent of all cases. Average values of the correlation coefficients are given in Table 5. These results confirm earlier investigations (Van der Hoeven *et al.*, 1973). Higher order regression lines did not reduce the residual least squares error significantly.

(c) Inaccuracy of the derived values: The accuracy of the slope m is directly related to the correlation coefficient, and related to both the range and number of x-values from which the regression line is calculated. We found, as an average, that the inaccuracy of the slopes of all individual regression lines within a group is a factor 4 to 5 less than the standard deviation of the total population of that group. Therefore, we may disregard the error in the individual values of m.

The same reasoning applies to the error in the values $y_{(100)}$ and $y_{(130)}$. The mean residual errors about regression are in the range 3 to 6 ms (see Table 5) and the standard deviations of the systolic intervals within all classes is in the range 7 to 19 ms (see Table 4). Since the average heart rate is always in the range 100 to 130 bpm a possible error in the slope will not contribute much to the error of $y_{(100)}$ or $y_{(130)}$. This would be the case if we had chosen a standardised heart rate far outside the average heart rate (say, at x=0 bpm).

(d) Interindividual differences within each class of subjects: The mean parameter values presented in Table 4 are calculated by simply adding all individual values. When there were large interindividual differences in the accuracies of the values, weighting factors should have been applied. We have tested this possibility, and the results were essentially the same, indicating that no large interindividual differences exist. Another reason is that individual errors are much less than the standard deviation of the population of a group, so we may conclude that the estimate of the individual values is good enough to find representative values of the class-values, and that no individual weighting of values is necessary.

REGRESSION EQUATIONS

Most investigators combine all individual data points and compute only one regression line for each class of subjects, for example, the regression line relating LVET and heart rate as published by Weissler *et al.* (1969) gives a quantitative relation between the LVET at a certain heart rate of one individual and those of a large group of other subjects at various heart rates. However, this regression line gives no information about how the LVET of that individual will change if his own heart rate changes as a result of drugs or exercise, for example. Our mean regression lines indicate how a certain systolic time interval will change as a function of heart rate for the average subject within a class.

QS_2 VERSUS HR

In this study, the QS_2 measurements of the normal subjects show an inverse relation with HR. A linear regression equation has been used, though the individual data suggest a slightly non-linear relation. This departure from the linear was so small over the relevant range (HR=90–140 beats/min) that a second order regression line gave no significant improvement. Kesteloot *et al.* (1968) came to the same conclusion, from their measurements on 267 normals, carried out in supine position at rest. Their regression equation (QS_2=493–1·5 HR) does not differ essentially from our results. Using phonocardiography, Strandell (1964) obtained regression lines between the interval S_1–S_2 (interval between the first and second heart sound) and HR during exercise in a sitting position. Though S_1–S_2 is a different time interval from the QS_2, which we used, there is a remarkable agreement with our findings: during exercise in the sitting position with stepwise increased work loads, S_1–S_2 at first decreased approximately linearly with increased HR but a slightly non-linear relation was found at higher rates.

LVET VERSUS HR

The LVET obtained from normals shows that the individual LVET relation was inversely linear to HR. This corresponds with the results of a great number of other investigators who also found such linear relations for groups of normals in the supine position at rest. Weissler *et al.* (1969), who carried out measurements in 121 normal male subjects in a supine position, found a mean regression line: LVET=–1·7 HR +413 (ms). Willems *et al.* (1970) found: LVET=–1·65 HR+419 (ms) as a mean regression line in 72 normals in the supine position at rest. A notable difference between Weissler's results obtained at rest and ours during exercise in the upright position is that the LVET is found to decrease less with rising heart rate. No subject in our normal groups shows an individual slope (m_{LVET}) steeper than –1·4, and the mean slope is –1·0 (±0·15). Maher *et al.* (1974) obtained regression equations relating STI to heart rate during submaximal supine exercise in a small group (10) of young physically active men. They found that the slopes for the LVET (also QS_2) with the increase in heart rate were nearly identical to the regression equations of Weissler. It seems probable that the differences in results obtained by Maher *et al.* and our group are caused by the difference in position (supine or upright) of the normal subjects. This requires further investigation.

PEP VERSUS RR

An important observation based on the measured data is the linearity of individual relations when PEP is plotted as a function of RR interval. This simplifies the data handling as compared with the necessity of calculating a second order regression line if PEP is given as a function of HR. This result confirms a preliminary investigation (Van der Hoeven *et al.*, 1973). Fabian *et al.* (1972a) calculated an equation for PEP versus HR through data points obtained from 50 normal subjects, in the supine position at rest; the coefficients were of the same order as Weissler's findings. However, Fabian indicated a very poor correlation (–0·30) between PEP and HR, while Weissler gave no information on this item. Our data show a distinct relation between PEP and RR interval for each individual with a high mean correlation coefficient of 0·92.

VARIANCE IN MEASUREMENTS

The individual regression lines as presented in this study are characterised by a high mean correlation coefficient and relatively low standard deviations about regression. Other work suggests that the measuring circumstances may influence such results drastically; in particular, data obtained at rest are very dependent on physical and physiological factors. When measurements have been taken during breaks in an exercise period, the results of a number of studies indicate a relatively large individual spread. Pouget *et al.* (1971) found, for 20 normals after exercise at a heart rate of 87 beats/min, a group standard deviation in LVET of $\sqrt{20} \times 5{\cdot}7 = 25$ ms; the present investigation yields a group standard deviation of only 9 to 13 ms for $LVET_{(100)}$. The results of McConahay *et al.* (1972) and Agress *et al.* (1965) on measurements taken several seconds after exercise show such a large spread that those workers conclude that their results cannot be used to separate patients from normals. Using a method, comparable to ours, Pigott *et al.* (1971) found a spread which is about the same as that of our present study.

The length of the LVET is determined by various factors, such as preload, afterload, myocardial inotropy, and heart rate (Shaver *et al.*, 1968; Sultan Ahmed *et al.* 1972). During a subject's transition from exercise to rest, all these factors will change, thus contributing to large variations in the LVET. Continuous recording during and after exercise indicated that during the first minute after exercise the heart rate in a group of normal subjects fell at a rate between 0·25 and 1·1 bpm/s. However, the LVET decreases at a relatively much faster rate. This is illustrated in Fig. 6, which gives LVET as a function of HR for two subjects A and B. The upper regression lines are calculated according to the procedure described in this paper. At the end of the exercise test the subjects stopped pedalling but the recording continued. The lower re-

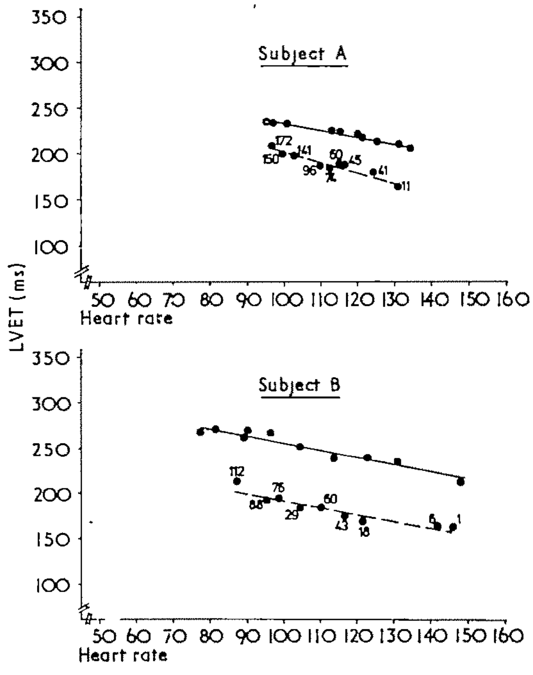

Fig. 6 *LVET as a function of HR for two subjects A and B. The upper lines in each plot are calculated through all data points obtained during increasing exercise load. The lower lines are calculated through the data points obtained during the transition from exercise to rest. Next to the data points is indicated the time in seconds elapsed since pedalling was stopped. Observe the almost immediate drop in LVET and the gradual return of HR back to resting values.*

gression lines are calculated through the data points obtained during this exercise-to-rest transition period; the time in seconds which elapsed after pedalling was stopped is indicated for each point. The regression lines derived after exercise are shifted downwards significantly. The LVET shortens rapidly after cessation of the exercise; moreover, a considerable difference between the shortening in the two subjects is apparent (40 and 60 ms). In the study of STI in relation to exercise, therefore, it is recommended that only data obtained during *uninterrupted* exercise be used.

Other factors which will contribute to a uniform response, with small intra-individual variations are as follows: increase of exercise load at a low rate so that the measurements are obtained virtually during a steady state; decrease of beat-to-beat variations in RR interval at heart rates above 100 bpm, which will reduce the beat-to-beat variations in the STI values; stroke volume, which is one of the determining factors of LVET, will reach a maximum at heart rates of approximately 110 bpm (Åstrand *et al.*, 1964). This stabilisation will decrease the beat-to-beat variations in LVET.

DIFFERENCES BETWEEN GROUPS

In Table 4 the significance of the differences between the values of different groups is indicated.

The most striking difference between the two normal groups is given by the QS_2 values, which is probably the result of a difference in PEP, the young normal subjects having a PEP which is 10 ms shorter. Using the S_1–S_2 interval, Strandell (1964) established similar differences between his older and younger groups. In addition, the differences between the two patient groups are striking. This is specially true of the relation between LVET and HR which turns out to be important in separating patients with coronary insufficiency but normal ventriculograms (P_1) from those with an abnormal left ventriculogram (P_2). The P_1 group has longer LVET corrected for heart rate, but the P_2 group has a considerably shorter LVET as compared with the normal groups.

In both patient groups we found a considerable lengthening of the PEP, the P_2 group showing the longest PEP. In the P_2 group the short LVET is compensated by a long PEP, resulting in almost normal QS_2 values. Only the slope m_{QS2} of the P_2 group differs significantly from that of the older group of normals ($N_{>40}$) (see also Fig. 4).

CORRELATION WITH EJECTION FRACTION

The ejection fraction (EF) is considered to be a measure of left ventricular function, and it is relatively easy to calculate this fraction from the left ventriculogram. In Fig. 7 the EF is plotted as a function of $\mathrm{PEP}_{(100)}/\mathrm{LVET}_{(100)}$ for those patients for which the EF could be estimated. The ejection fraction of the P_2 group is found to be significantly lower than that of the P_1 group ($P < 0{\cdot}001$). If both groups are combined, a statistically significant correlation of $-0{\cdot}51$ between $\mathrm{PEP}_{(100)}/\mathrm{LVET}_{(100)}$ and the EF is found. In the same subjects the correlation of the systolic ratio $\mathrm{PEP}_{(100)}/\mathrm{LVET}_{(100)}$ with end-diastolic volume or with stroke volume was much lower.

These results confirm those reported by Vonk and Clerens (1974), who, in addition, found an average EF of 0·67 (SEM=0·05) for a small group of 8 normal subjects.

From the results given in Table 4, the following conclusions may be drawn concerning the differentiation of the subjects in the various groups:

(A) P_2 SUBJECTS

P_2 subjects are characterised by a low value of $\mathrm{LVET}_{(100)}$ and a high value of $\mathrm{PEP}_{(100)}$, so that the ratio $\mathrm{PEP}_{(100)}/\mathrm{LVET}_{(100)}$ of the P_2 subjects is high. Indeed, all but 6 P_2 patients have a ratio higher than 0·46; all the normal subjects, both old and young, and all but 3 P_1 patients have a ratio lower than 0·46 (Fig. 5). Since the correlation within groups between $\mathrm{PEP}_{(100)}$ and $\mathrm{LVET}_{(100)}$ is low, both characteristics (raised $\mathrm{PEP}_{(100)}$ and depressed $\mathrm{LVET}_{(100)}$) have to be present for a subject to be classified as a P_2 subject.

Only 16 per cent of all normal subjects have a ratio of $\mathrm{PEP}_{(100)}/\mathrm{LVET}_{(100)}$ higher than 0·40; 88

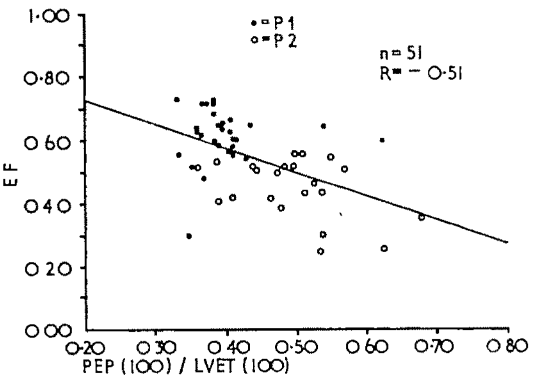

Fig. 7 *Relation between PEP/LVET at a heart rate of 100 and the ejection fraction at rest. Data points are from the 51 subjects of the P_1 and P_2 patient groups. Correlation equals $-0{\cdot}51$, and differs significantly from zero with $P<0{\cdot}0005$*

per cent of all P_2 subjects and 40 per cent of P_1 subjects exceed that value. We may conclude that a ratio over 0·46 suggests coronary insufficiency and that a ratio over 0·45 is related to ventricular dysfunction which results in a poor contraction pattern with long PEP values and a reduced ejection time. The high mean value of $PEP_{(100)}/LVET_{(100)}$ for the P_2 group coincides with a low mean ejection fraction at rest.

(B) P_1 SUBJECTS

P_1 patients are characterised by a relatively high value of $LVET_{(100)}$ and a low value of $-m_{LVET}$, so that the index $LVET_{(100)}/m_{LVET}$ is high for P_1 subjects. For all but 10 P_1 subjects the value $LVET_{(100)}/-m_{LVET}$ exceeds 280 bpm[1].

However, it is not only P_1 patients who have a high index $LVET/-m_{LVET}$, as young normal subjects also tend to have an index which is higher compared with the old normal group. We might postulate that young normal subjects compensate for a relatively short ejection time by a high outflow velocity, which is related to a short PEP and a high rate of rise of left ventricular pressure. Therefore, we may incorporate PEP as an extra value, since young normal subjects have a PEP which is significantly lower than the PEP for all other classes. This leads to an attempt to try:

$$\frac{LVET_{(100)}+PEP_{(100)}}{-m_{LVET}}=\frac{QS_{2(100)}}{-m_{LVET}}$$

for its ability to separate the groups. As can be seen in Fig. 4, the difference in QS_2 between the P_1 group and the other groups increases for increasing heart rates, which indicates an influence of the slope m_{QS_2}. The difference especially in QS_2 between the old normal subjects and P_1 increases because of steeper slope m_{QS_2} for $N_{>40}$.

Incorporating the influence of the slope m_{QS_2} is achieved by taking the value $QS_{2(130)}$ instead of $QS_{2(100)}$. Applying linear classification theory to the data points indicates that a suppression of the zero-QS_2 point will improve the separation power. Therefore, the index

$$\frac{QS_{2(130)}-230}{-m_{LVET}}$$

is obtained as an index for separation of P_1 patients from normal subjects. Individual values of this index for all subjects are given in Fig. 5. If this index exceeds the value of 75 bpm, the subject is identified as a P_1 patient.

In order to test the reproducibility of the results, 6 subjects, 4 from the group of young normals, and 2 from the old normal group, repeated their exercise test after a time span from one week to several months. The results in terms of the individual identifying indices are given in Table 6; each subject is assigned to the same (normal) group as before. The number of repeated tests is small; a large group of both patients and normals will have to be investigated in order to determine the reproducibility of identification according to appropriate groups using the indices desired.

The intraclass correlations between the indices $PEP_{(100)}/LVET_{(100)}$ and $QS_{2(130)}-230)/-m_{LVET}$ is for all classes less than 0·41 (average: 0·31), which is sufficiently low to regard these two indices as having an independent information content. The intraclass correlation of $PEP_{(100)}/LVET_{(100)}$ and $PEP_{(130)}/LVET_{(130)}$ is more than 0·76 (average 0·81) for all classes.

This indicates that the choice of a standardised heart rate is not critical, as long as the heart rate does not differ too much from the average heart rate during the exercise test.

Conclusions

Heuristic classification rules were found for the separation of P_1 and P_2 subjects from the normal groups. We may summarise these rules as:

Rule 1: if $PEP_{(100)}/LVET_{(100)}$ exceeds the value 0·46 the subject is identified as a P_2 patient.

Table 6 *Results of repeated exercise tests*

Subject No.	*Age (y)*	$\frac{PEP_{(100)}}{LVET_{(100)}}$	$\frac{QS_{2(130)}-230}{-m_{LVET}}$ *(bpm)*
1	37	0·306	69
		0·343	74
3	27	0·329	57
		0·355	65
8	24	0 370	59
		0·362	44
16	22	0·316	67
		0 309	50
36	48	0 382	63
		0·394	68
53	41	0·454	54
		0·400	41

Abbreviations as in Table 3.

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[1] This ratio may be interpreted as the change in heart rate required for a 100 per cent change in LVET, since

$$\frac{LVET_{(100)}}{-m_{LVET}}=\frac{LVET_{(100)}}{\left(\frac{\Delta LVET}{\Delta HR}\right)}=\frac{\Delta HR}{\left(\frac{\Delta LVET}{LVET_{(100)}}\right)}$$

For a ratio of 280 bpm, this would mean, by a theoretical extrapolation of the regression line, that LVET will be zero at 100+280=380 bpm. A high index would indicate a slow adaptation of LVET to increasing heart rates.

For all remaining subjects the second rule applies:

Rule 2: if $(QS_{2(130)}-230)/-m_{LVET}$ exceeds 75 bpm the subject is identified as a P_1 patient.

If both conditions are not fulfilled, the subject is regarded as being normal.

These classification rules are applied to all subjects and the results are given in Table 7. As is indicated, in 86 per cent of all cases a correct classification is made. If we make the simplification of combining the two patient groups and look for the classification 'normal' or 'patient' (whether P_1 or P_2), in 93 per cent a correct classification is made. In the latter case, the 'Index of Merit' equals 0·80[1].

It should be noted that a second, independent, group of patients and normals needs to be analysed in order to test the merits of the above given classification system. Though data from a much larger group than that presented here (from other clinical centres or collected after the closure of this study) is available such a detailed evaluation has yet to be done.

From Table 7 it can be seen that 19 P_2 subjects are classified correctly. If we apply rule 2 (for P_1 classification) to the P_2 subjects, 11 of those 19 subjects have the characteristics of P_1 patients, and 8 subjects are classified as 'normal'. The average ejection fractions of these two subgroups are 0·39 and 0·49, respectively. This might be an indication that there is a relation between the assignment of a subject in one or both classes and the myocardial performance: fulfilling the criteria for both P_1 and P_2 patients is worse than doing so for a P_1 or P_2 patient alone.

The results of this study indicate that exercise systolic time intervals may provide valuable information for the assessment of cardiac patients. Besides the power of exercise STI to separate normals from patients, it has the ability to distinguish between patients with normal and those with abnormal ejection fractions, a distinction determined usually by means of the invasive method of left ventriculography.

Table 7 *Results of classification method*

Class	*Total No.*	*Classified as*			*Fraction correct negative*
		Normal	P_1	P_2	
$N_{>44}$	33	32	1	0	0·97
$N_{<44}$	18	18	0	0	1·00
					Fraction correct positive
P_1	36	7	26	3	0·72
P_2	25	4	2	19	0 76

Abbreviations as in Table 2.

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[1] The 'Index of Merit' is defined as the fraction correct negative + the fraction correct positive −1 = 0·98 + 0·82−1 = 0·80. If the classification follows a random assignment of subjects to two groups, the Index of Merit will be 0·5 + 0·5−1 = 0.

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Changes in systolic time intervals during treatment of diabetes mellitus

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The cardiovascular response to the control of diabetes by sulphonylurea drugs has been investigated using systolic time intervals in a group of 19 diabetics. Before treatment a significantly greater heart rate and shortening of QS_2 interval and left ventricular ejection time index were encountered among the more hyperglycaemic diabetic patients requiring drug therapy while all diabetics had a reduction of pre-ejection period index. There was a gradual return of resting heart rate and systolic time intervals to control values along with the fall in plasma sugar concentration during treatment. A likely explanation of the findings is that uncontrolled diabetics, particularly those more severely affected, are subjected to an increased adrenergic stimulus to the cardiovascular system which disappears with therapy. There is no evidence of positive inotropic action of sulphonylurea drugs in this study.

Since the publication of the University Group Diabetes Programme (Klimt *et al.*, 1970) which suggested an increase in mortality from cardiovascular disorders in those patients treated with tolbutamide, several workers have studied the effects of this drug on the heart *in vivo* and *in vitro*. The results have been confusing. Some authors have reported a positive inotropic effect (Hildner *et al.*, 1971; Palmer *et al.*, 1971; Lasseter *et al.*, 1972; Young *et al.*, 1975), while Crass *et al.* (1973) have shown that increased contractility is dose dependent and that above a certain concentration of tolbutamide negative inotropism results. Crockett *et al.* (1973, 1974) could not show any inotropic effect on the human heart in clinical studies despite increased contractility of both animal and human hearts *in vitro*. The majority of these were acute studies after parenteral administration of the drug.

In an attempt to resolve this conflict it was decided to examine changes in myocardial function during the first three months' treatment of diabetes. Two groups of diabetic patients were studied, one managed by diet and the other treated with diet and a sulphonylurea drug. Simultaneous recordings of the electrocardiogram, phonocardiogram, and carotid pulse were performed in order to obtain systolic time intervals (Weissler *et al.*, 1969). This technique has been used to study changes in myocardial contractility produced by cardiac glycosides, adrenergic and cholinergic drugs, and tolbutamide (Raab *et al.*, 1958; Weissler *et al.*, 1965; Harris *et al.*, 1967; Shapiro *et al.*, 1970; Crockett *et al.*, 1973). Martin *et al.* (1971) have shown that systolic time intervals correlate well with internal measurements of left ventricular function.

Patients and methods

Nineteen untreated male patients attending the diabetic clinic for the first time were studied. Nine patients were subsequently managed with diet alone and 10 with diet and a sulphonylurea drug. The severity of the diabetes determined treatment. A random plasma sugar level greater than 14 mmol/l (252 mg/100 ml) usually indicated the need for hypoglycaemic compounds. Each individual was seen again 1 month and 3 months after starting treatment. At each attendance the plasma sugar concentration, weight, and systolic time intervals were measured. Recordings of the full electrocardiogram and the blood pressure were made on every patient at the first visit. Systolic time intervals were obtained by using a Mingograph 3-channel recorder (Elema-Schonander) modified to reproduce simultaneously the electrocardiogram, phonocardiogram, and carotid pulse wave at a paper speed of 100 mm/s. From these tracings were derived the QS_2 interval—from the start of the QRS complex to the start of the aortic second sound, the left ventricular ejection time (LVET)—from the start of the upstroke of the carotid pulse to the incisura, and the

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pre-ejection period (PEP) which is the difference between the QS$_2$ and LVET. The mean values of 10 complexes were obtained for each measurement. The QS$_2$, LVET, and PEP results were then corrected for heart rate using the regression equations of Weissler *et al.* (1969). The PEP/LVET ratio was calculated using the uncorrected values of PEP and LVET.

Seven patients in the diet group and 8 of those who needed an oral hypoglycaemic drug had normal electrocardiograms. Two patients in the drug treated group and 2 controlled by diet showed ischaemic ST depression.

Of those in the sulphonylurea drug group 7 patients received glibenclamide and 3 tolazamide. The dosages of the drugs were in the therapeutic range in each case. Three patients on glibenclamide received 10 mg daily and 2 were on 5 mg a day. The doses in the remaining 2 patients on this drug were 2·5 mg and 20 mg, respectively. In the tolazamide treatment group 1 patient received 250 mg daily while the remaining 2 were on 350 mg daily. No patient in the study was given any other medication.

The mean age of each group was similar.

Twenty-seven ambulant male volunteers with clinically normal hearts and blood pressures were investigated in an identical manner to provide control data. They all had normal electrocardiograms, plasma sugar concentrations, and their mean age and weight were similar to those of the diabetic groups.

To avoid any errors resulting from a possible diurnal variation of systolic time intervals, all measurements in the 19 diabetics and 27 control subjects were made between 14·00 and 16·00 hours.

Results

Tables 1 and 2 show the results.

The resting heart rate before treatment was greater among the more hyperglycaemic diabetic patients needing both sulphonylurea drugs and dietary restriction, when compared with the control subjects ($P < 0{\cdot}01$). The difference was still apparent 1 month after starting drug therapy but was no longer significant at 3 months. The heart rate of diabetic patients managed with dietary restriction alone showed no significant difference from the other two groups either before therapy or at the subsequent visits.

There was a small but significant shortening of the rate corrected QS$_2$ interval (QS$_2$I) in the drug treated patients before therapy when compared with the control group ($P < 0{\cdot}001$). There was a gradual lengthening of the QS$_2$I at succeeding visits. It remained less than the control value at 1 month ($P < 0{\cdot}02$) but finally no difference was shown between the control subjects and the drug-treated diabetics (Fig. 1).

The diet group, however, behaved differently. There was no abnormality of the QS$_2$I when the three measurements were compared with each other and with those of the control group. However, a lengthening of the QS$_2$I occurred within the diet group when paired differences were analysed ($P < 0{\cdot}05$).

Although before treatment significant shortening of the rate corrected PEP (PEPI) was absent when the two groups of diabetics were considered separately the PEPI of all 19 diabetics was 113 ms (standard deviation 15·9). This was less than the control value ($P < 0{\cdot}05$). During the study lengthening of the PEPI occurred as shown by a paired 't' test ($P < 0{\cdot}02$) and at the final visit the PEPI of diabetics and control subjects was similar. Before treatment there was shortening of the rate corrected LVET (LVETI) in the drug treated group when compared with the diet and control groups ($P < 0{\cdot}05$ and $P < 0{\cdot}02$, respectively). During the study lengthening of the LVETI occurred within the

Table 1 *Data for diabetic patients at each visit compared with those of control group (±1 SD)*

	Diet group *1st visit* *(9)*	*2nd visit* *(9)*	*3rd visit* *(9)*	*Tablet group* *1st visit* *(10)*	*2nd visit* *(10)*	*3rd visit* *(10)*	*Control group* *(27)*
Age (y)	53·6 ±13·1	—	—	52·4 ±6·8	—	—	50·9 ±9·4
Weight (kg)	82·6 ±15·0	82·0 ±14·9	78·8 ±13·9	74·7 ±10·1	74·5 ±11·5	74·6 ±13·0	75·3 ±13·1
Heart rate (b/min)	72·6 ±10·3	75·2 ±11·6	73·6 ±10·5	81·5 ±11·2	80·9 ±10·3	76·5 ±8·5	68·8 ±11·0
Systolic blood pressure (mmHg)	141 ±13·6			151 ±14·5			132 ±16·8
Diastolic blood pressure (mmHg)	84·4 ±7·7			89·5 ±10·1			81·9 ±12·3
Plasma sugar concentration (mmol/l)	11·0 ±3·1	8·2 ±2·1	8·2 ±1·5	18·6 ±3·0	8·4 ±2·0	6·8 ±2·3	5·7 ±1·1

Table 2 *Mean corrected QS_1 interval, corrected LVET, corrected PEP, and PEP/LVET in control group and at each visit (±1 SD)*

	Diet group			*Tablet group*			*Control group*
	1st visit (9)	*2nd visit (9)*	*3rd visit (9)*	*1st visit (10)*	*2nd visit (10)*	*3rd visit (10)*	*(27)*
Corrected QS_1 interval (QS_1I)	523 ±15·6	526·5 ±17·2	533·4 ±12·5	503·3 ±25·9	513·6 ±20·1	529·9 ±17·6	527·8 ±12·2
Corrected PEP (PEPI)	113·9 ±13·2	117·9 ±8·7	125·1 ±14·6	112·3 ±18·7	114·3 ±15·1	118·8 ±21·2	122·5 ±14·6
Corrected LVET (LVETI)	409·1 ±18·4	409·3 ±16·7	408·2 ±18·2	391·3 ±13·5	399·4 ±14·1	411·3 ±9·4	405·4 ±14·6
PEP/LVET ratio	0·30 ±0·061	0·31 ±0·039	0·34 ±0·071	0·32 ±0·075	0·31 ±0·061	0·31 ±0·079	0·33 ±0·06

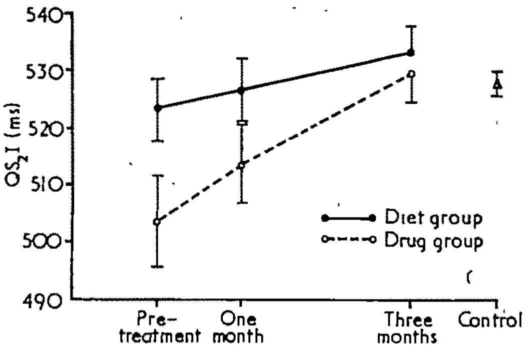

Fig. 1 *Mean corrected QS_1 interval (QS_1I) ± 1 SEM in the two diabetic treatment groups with control values for comparison.*

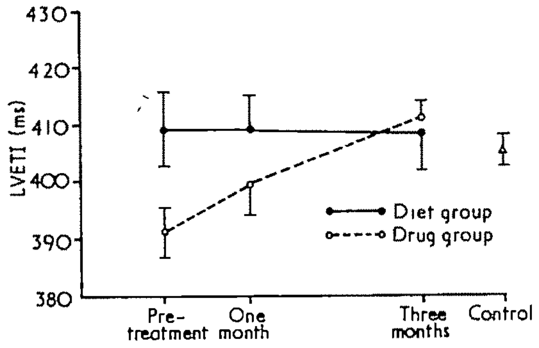

Fig. 2 *Mean corrected left ventricular ejection time (LVETI) ±1 SEM in the two diabetic treatment groups with control values for comparison.*

tablet group ($P < 0·001$). The patients on dietary control showed no difference either when considering the group as a whole or when paired differences were analysed (Fig. 2).

The PEP/LVET ratio showed no significant deviation from control values in any of the diabetic patients throughout the study.

There were high plasma sugar concentrations in both the diabetic groups at the first visit when compared with the control values ($P < 0·0005$). The levels were greater in the drug treated patients, as therapy was determined by the initial severity of the diabetes. After 1 month the plasma sugar concentrations in both diabetic groups had fallen but were still higher than those of the control series ($P < 0·0005$). At the final visit the mean plasma sugar level of the diet group remained greater than the control values ($P < 0·005$) but that of the drug treated patients occupied an intermediate position and was not statistically different from those of the other two groups.

Although the mean weights of the patients were similar at each visit a paired 't' test showed a reduction in weight during the study in the diet treated group ($P < 0·05$) but not in the individuals on oral hypoglycaemic drugs.

Blood pressure was measured at the initial visit. The systolic pressure was significantly higher in the group needing sulphonylurea drugs when compared with the control values ($P < 0·01$), but the patients requiring diet alone showed no significant difference from the other two groups. The diastolic blood pressure was similar in all three groups.

Discussion

The small but significant cardiovascular changes shown among diabetic patients appeared to be related to the severity of the underlying hyperglycaemia in that they were present to their greatest extent in diabetic patients with sugar levels high enough to require sulphonylurea drugs in addition to dietary restriction. Under the influence of therapy there was a gradual return to control values of both heart rate and systolic time intervals accompanying the reduction in plasma sugar though the biochemical improvement was somewhat faster than the haemodynamic.

One possible explanation of the observed cardiovascular changes could be an increased adrenergic stimulus more obvious in the hyperglycaemic diabetic. Adrenaline produces a reduction of PEP and QS_2 (Raab *et al.*, 1958; Harris *et al.*, 1967; Martin *et al.*, 1971). Raab *et al.* (1958) have also found a shortening of QS_2 (total electromechanical systole) and LVET with adrenaline. Such a mechanism has been suggested to explain the shortening of the QS_2 interval after myocardial infarction (Lewis *et al.*, 1972). Certainly a rise in catecholamines, notably noradrenaline, is known to occur when diabetes is out of control (Christensen, 1974). None the less, at the second visit when satisfactory control of diabetes was obtained a fall in circulating catecholamines would have been expected to occur, and hence a return of the systolic time intervals to normal, whereas systolic time intervals were still significantly shortened.

Another possible mechanism which may explain the reduction in the LVETI is lipid deposition within the myocardial cells reducing the compliance and thus the stroke volume. Animal studies have shown cholesterol and triglyceride deposition within the myocardium in alloxan-induced diabetes (Regan *et al.*, 1974). If excess lipids were present within the myocardium, a situation similar to a restrictive cardiomyopathy would develop. The LVET has been shown to shorten in this type of cardiomyopathy. However, lengthening of the PEP and increase in the PEP/LVET ratio also occur as would be expected in any situation where myocardial contractility is reduced (Khullar and Lewis 1976; Ghose *et al.*, 1976). Such a mechanism would not, therefore, account for the initial shortening of PEP encountered in the present state.

Relatively high systolic blood pressure among the more severely hyperglycaemic group would tend to lengthen rather than shorten the LVET (Braunwald *et al.*, 1958; Shaver *et al.*, 1968), and the diastolic pressures were similar in all three groups of patients.

The purpose of the study was to examine the possibility that sulphonylurea drugs may have an overall positive inotropic effect on the myocardium when used in the management of diabetes. Our results appear to show that this is not so. The drug-treated group had a significant lengthening of LVETI during the period of treatment towards the values obtained among the control subjects and all diabetics showed an increase in PEPI. This is the reverse of the shortening of these time intervals with positive inotropic drugs such as cardiac glycosides (Weissler *et al.*, 1965; Shapiro *et al.*, 1970).

It seems likely that the changes in cardiovascular behaviour with control of diabetes are too complex to ascribe any result to a single intervention such as drug administration. If the changes observed in this study are the result of the withdrawal of an increased adrenergic stimulus to the heart which occurs in the untreated state, this may have clinical significance and could explain the improvement in angina which can occur after administration of the sulphonylurea (Singh and Bardhan, 1959). At all events we have found nothing to suggest that the particular sulphonylurea drugs studied produce a positive inotropic effect potentially hazardous in the management of patients with diabetes.

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Echocardiographic evaluation of left-to-right shunt in ventricular septal defect and persistent ductus arteriosus[1]

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Forty-five patients with either a ventricular septal defect or a persistent ductus arteriosus were assessed by echocardiography and cardiac catheterisation. Left atrial dimension was expressed either as a function of the body surface area (LAD cm per m² BSA), or as a multiple of the aortic root dimension (LAD/AR), and was compared with the shunt size as determined by oximetry. A highly significant ($P<0.001$) regression relation was found for the group as a whole. A significant relation also existed for each individual group: ventricular septal defect, ventricular septal defect with pulmonary hypertension, and persistent ductus arteriosus. Regression equations were derived for the whole group. The value of echocardiography is in separating large from small shunts and in adding a dimension to the follow-up of the individual patient.

The measurement of the size of left-to-right shunts at either ventricular or aortopulmonary level has traditionally depended on the use of oxygen saturations or of an indicator such as indocyanine green, at cardiac catheterisation. More recently, the use of radionuclide angiography with injection of tracer into a peripheral vein has been shown to give comparable results (Maltz and Treves, 1973; Alderson *et al.*, 1975).

In ventricular septal defect and in persistent ductus arteriosus an increased amount of blood is returned to the left atrium. Changes in volume of this chamber have been shown to occur in various haemodynamic disorders (Hawley *et al.*, 1966). Echocardiography has proved itself as a non-invasive method for determination of left atrial size with a high degree of accuracy. Measurements correlate closely with those obtained by angiography (Hirata *et al.*, 1969; Lundstrom and Mortensson, 1974; Ten Cate *et al.*, 1974; Yabek *et al.*, 1976). The larger the left-to-right shunt, the greater the volume of blood delivered to the left atrium. We designed this study to determine whether there is a relation between the magnitude of the shunt and left atrial size determined echocardiographically.

Subjects and methods

All children undergoing diagnostic cardiac catheterisation at The Hospital For Sick Children, Toronto, with a presumptive diagnosis of either ventricular septal defect or persistent ductus arteriosus were studied by echocardiography during the 24 hours preceding catheterisation. Forty-five patients were investigated, including 35 with ventricular septal defect and 10 with persistent ductus arteriosus. The haemodynamic and echocardiographic measurements are shown in Tables 1 and 2, respectively. Twelve of the patients with ventricular septal defect had pulmonary arterial systolic pressures greater than 40 mmHg.

CATHETERISATION METHODS

The size of the left-to-right shunt was determined by oximetry, using a Waters oximeter, and was expressed as pulmonary/systemic flow ratio. Oxygen consumption was assumed, using the tables of Lafarge and Miettinen (1970). The superior vena caval oxygen saturation was used for the mixed venous value, two samples usually being obtained from this site. All saturations were obtained consecutively, with the patient in a steady state. Any patient with angiographic and/or oximetric evidence of a significant left-to-right shunt at atrial level was excluded from the study.

ECHOCARDIOGRAPHIC METHODS

Commercially available ultrasonoscopes (Ekoline 20 or Hoffrell 101) were interfaced to a Cambridge Recorder. A variety of ultrasound transducers

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varying in frequency from 5 MHz (0·25 inch unfocused) to 2·25 MHz (0·5 inch focused at 5 cm) were used. The mitral valve echo was identified and a sweep then made by rotating the transducer superiorly and medially until the aortic root and left atrial wall were identified (Fig. 1). Only those patients in whom these structures were clearly shown were included in the study. Measurements were made as described by Brown *et al.* (1974). The left atrial dimension was measured at end-systole from the anterior edge of the posterior left atrial wall to the anterior edge of the posterior wall of the aortic

Table 1 *Haemodynamic and echocardiographic data in patients with ventricular septal defect*

Case No.	*Age at time of study*	*Aortic pressure (mmHg) (mean)*	*LV pressure (mmHg)*	*MPA pressure (mmHg) (mean)*	*RV pressure (mmHg)*	*LA mean pressure (mmHg)*	*Pulmonary/systemic flow ratio*	*LA dimension (cm per m^2 BSA)*	*LAD/AR*
1	11 y	105/56 (75)	105/6	34/14 (24)	34/2	11 (w)*	1.4:1	3·9	1·6:1
2	12 y	108/78 (95)	118/7	20/7 (14)	20/6	10	1·6:1	2·6	1·1:1
3	7 m	80/44 (60)	80/9	70/15 (44)	70/5	9	3·8:1	10·4	1·9:1
4	3 m	95/45 (70)	95/10	75/45 (60)	75/12	7	2:1	9·5	1·9:1
5	2 y	95/48 (72)	96/9	28/6 (14)	40/0	3	2:1	7·7	1·9:1
6	4 y	116/63 (85)	—	25/8 (18)	32/4	8 (w)	1·5:1	5·0	1·6:1
7	6 y	104/65 (85)	104/15	30/12 (14)	33/3	8 (w)	2:1	4·3	1·6:1
8	4 m	102/50 (80)	102/10	40/16 (30)	40/5	—	2·8:1	6·5	1·7:1
9	12 y	105/65 (83)	105/10	27/9 (18)	35/10	—	1:1	2·5	1·2:1
10	2 y	100/65 (82)	100/10	30/10 (18)	58/8	5	1·6:1	4·8	1·3:1
11	1 y	95/55 (73)	95/10	48/25 (35)	50/2	—	3:1	6·0	1·5:1
12	1½ m	90/45 (60)	90/10	55/15 (30)	55/5	5	3·4:1	7·7	1·7:1
13	1½ y	85/55 (73)	85/6	23/7 (13)	23/3	3	1·1:1	7·9	1·5:1
14	9 y	—	94/2	20/7	20/0	3	1·4:1	2·4	1·2:1
15	4 m	90/65 (80)	90/8	45/15 (25)	45/6	8	4·3:1	6·5	1·4:1
16	4 m	72/40 (54)	72/5	40/10 (22)	43/3	4	4·2:1	6·8	1·8:1
17	3 m	65/44 (55)	65/9	50/20 (39)	50/5	7	5:1	9·6	2:1
18	4 m	83/49 (65)	88/6	55/20 (33)	60/7	8	5·2:1	13·2	2·5:1
19	2½ y	—	92/1	49/11 (22)	40/2	—	1·9:1	4·2	1:1
20	2 y	92/58 (76)	92/1	18/8 (10)	22/2	7 (w)	1·1:1	2·8	1·3:1
21	14 y	100/65 (82)	115/15	51/16 (32)	52/8	—	1·5:1	3·0	1·6:1
22	5 m	85/45 (62)	85/10	45/14 (28)	48/7	9	2·3:1	7·6	2·3:1
23	1 y	79/50 (62)	—	20/7 (14)	20/4	7 (w)	1·8:1	4·2	1:1
24	2½ y	95/52 (67)	95/5	26/7 (14)	26/3	6	1·6:1	4·0	1·3:1
25	2 m	55/34 (44)	55/8	44/16 (26)	44/3	16	4:1	9·0	2·1:1
26	2 m	85/40 (60)	85/10	35/7 (18)	50/5	—	2:1	11·8	2:1
27	7½ y	110/76 (96)	110/10	27/7 (13)	31/2	14	2·2:1	3·3	1·8:1
28	8 y	105/70 (75)	105/10	105/60 (80)	105/10	9	1:1	2·5	1:1
29	7 y	92/50 (71)	—	89/48 (64)	89/3	—	0·65:1	2·7	1:1
30	8 y	74/45 (67)	74/4	39/14 (28)	76/4	10	1·9:1	2·7	1:1
31	3 y	95/50 (65)	95/5	30/12 (22)	54/4	8	2·2:1	6·7	1·1:1
32	5 y	109/75 (93)	109/3	—	90/4	—	1·3:1	3	1:1
33	2 m	75/45 (55)	75/10	75/32 (53)	75/5	11	3·8:1	8·3	1·6:1
34	10 y	100/80 (30)	100/9	100/70 (82)	100/6	6	1·4:1	2·8	1·4:1
35	6 y	94/52 (70)	94/6	22/12 (16)	40/4	—	1:1	2·6	1·3:1

*w = PA wedge.

Table 2 *Haemodynamic and echocardiographic data in patients with persistent ductus arteriosus*

Case No.	*Age at time of study*	*Aortic pressure (mmHg) (mean)*	*LV pressure (mmHg)*	*MPA pressure (mmHg) (mean)*	*RV pressure (mmHg)*	*LA mean pressure (mmHg)*	*Pulmonary/systemic flow ratio*	*LA dimension (cm per m^2 BSA)*	*LAD/AR*
1	3 y	96/52 (75)	96/6	18/6 (10)	18/3	—	1·2:1	3·9	1·6:1
2	1 y	93/42 (65)	—	30/10 (20)	31/4	11 (w)*	2·5:1	5·4	1·5:1
3	4 y	90/58 (77)	96/4	22/12 (14)	22/2	12	1·5:1	3·6	1·5:1
4	4 m	85/40 (58)	—	21/10 (16)	30/5	—	2·7:1	8·3	2·3:1
5	9 d	—	60/3	30/10	32/2	4	2·3:1	5·7	1·3:1
6	1 y	98/60 (75)	85/5	25/8 (15)	25/3	7	2·3:1	5·6	1·6:1
7	7 m	102/40 (70)	115/10	72/30 (46)	72/6	9	2·3:1	5·9	1·9:1
8	4 y	114/78 (96)	—	23/7 (14)	23/2	2	1·2:1	5·9	1·4:1
9	2 y	101/56 (81)	—	30/19 (23)	30/3	—	3:1	6·4	2·5:1
10	2½ y	95/45 (65)	95/5	35/10 (22)	60/3	—	1·7:1	5·6	1·9:1

*w = PA wedge.

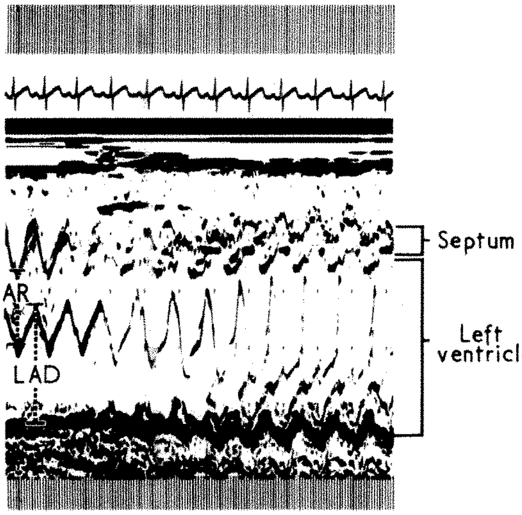

Fig. 1 *Typical sweep showing method of measuring left atrial dimension (LAD) and aortic root (AR) size in a patient with ventricular septal defect (pulmonary systemic flow ratio 1·5 : 1).*

root. The aortic root was measured at end-diastole from the anterior edge of the anterior aortic wall to the anterior edge of the posterior aortic wall. The posterior left atrial wall was identified as that echo which is continuous with the epicardial echo seen behind the left ventricular posterior wall (Fig. 1). Measurements of the left atrial dimension and aortic root were made independently by two observers: any dimension variation of greater than 1 mm was checked. The left atrial dimension was expressed as a function of the body surface area (LAD cm per m^2 BSA) and as a multiple of the aortic root dimension (LAD/AR). The body surface area was determined from measurements of the height and weight using a standard nomogram (Diem and Lentner, 1970).

STATISTICAL ANALYSIS

The relation between LAD/AR or LAD and the shunt size determined by oximetry was established by linear regression. The significance of the resulting regression equation was assessed by the analysis of variance technique. These two regression relations were established and assessed for each group of patients separately and combined.

Results

The statistical analysis for all patients shows a significant relation between the left atrial dimension and the size of the left-to-right shunt ($P < 0·001$) (Fig. 2 and 3).

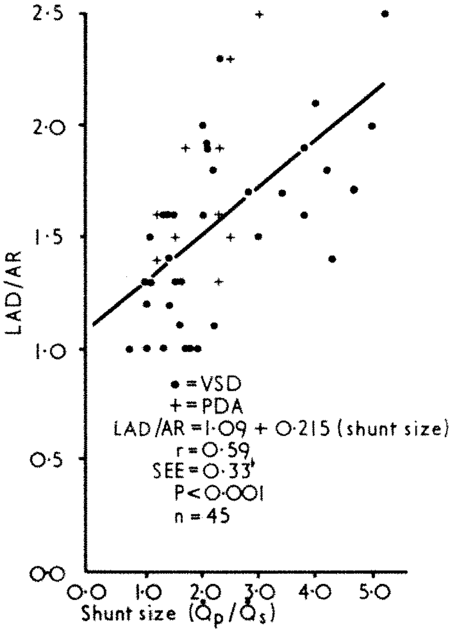

Fig. 2 *Results for all patients showing the relation between LAD/AR and shunt size. SEE = standard error of the estimate. Other abbreviations as in text.*

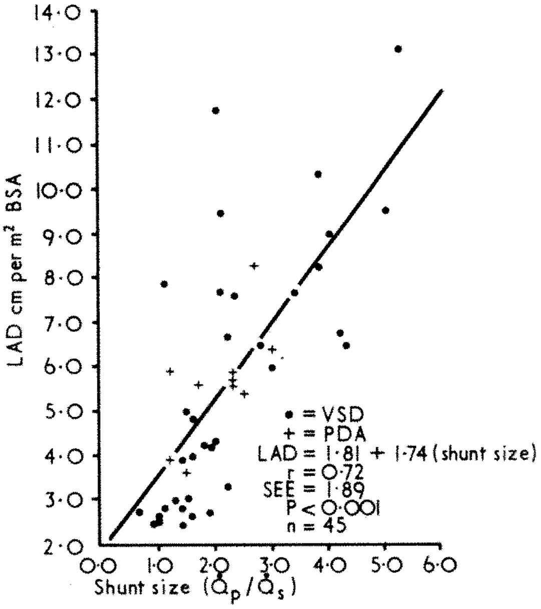

Fig. 3 *Results for all patients showing the relation between left atrial dimension and shunt size. All abbreviations as before.*

Each group was then considered separately (Table 3). In all groups the LAD had a higher positive correlation with the shunt size than the LAD/AR. A particularly high correlation was found in the pulmonary hypertensive group. This group included infants with large left-to-right shunts through a ventricular septal defect as well as older children with high pulmonary vascular resistances. The high correlation in this group confirms the validity of this method of assessment of all haemodynamic types of ventricular septal defect.

The statistical correlation is lower in persistent ductus arteriosus (Table 3). The shunt in persistent ductus arteriosus is distal into the pulmonary artery. It is, therefore, difficult to obtain a sample of blood that reflects adequate mixing. Streaming may result in either too high or too low oxygen saturation values being obtained by oximetry. This additional inaccuracy is the probable reason for the low correlation in this situation.

Table 3 *Statistical analysis*

Group	*Number*	*LA dimension*	*r*	*Significance level of regression P*
All patients	45	LAD/AR	0·59	< 0·001
		LAD*	0·72	< 0·001
All patients with VSD	35	LAD/AR	0·65	< 0·001
		LAD*	0·73	< 0·001
VSD with normal pulmonary artery pressure	23	LAD/AR	0·42	< 0·05
		LAD*	0·43	< 0·005
VSD with pulmonary hypertension	12	LAD/AR	0·78	< 0·005
		LAD*	0·83	< 0·001
PDA	10	LAD/AR	0·6	< 0·10
		LAD*	0·66	< 0·05

*LAD related to body surface area (cm per m^2 BSA).

The regression equations were calculated from the data on all 45 patients, and are shown with the standard error of the estimate (SEE):

LAD = 1·81 + 1·74 (shunt size). SEE 1·89
LAD/AR = 1·09 + 0·215 (shunt size). SEE 0·33

Our results imply that a higher positive correlation will be obtained if the LAD is used rather than the LAD/AR. Problems may exist in the premature infant and newborn with the former determination; this is considered in the discussion.

Discussion

A significant relation exists between the LAD/AR or LAD and the calculated shunt size. These correlations are low, but are similar to those found when results obtained using a dye dilution method (Bloomfield, 1974) or a radionuclide technique (Maltz and Treves, 1973) are compared with results from blood oxygen saturation data. The low correlation is probably a result of the inaccuracy of the shunt calculation from oxygen saturation data obtained by oximetry (Schostal *et al.*, 1972). This is compounded by some inaccuracies inherent in the echocardiographic technique.

These problems in echocardiographic assessment should be considered. The left atrial dimension does not increase linearly with body surface area (Goldberg *et al.*, 1975). Small and premature infants will have very large left atrial dimensions, if these are expressed in terms of body surface area; one should probably use the LAD/AR in this group. The use of this ratio to assess shunt size has been shown to have clinical application in premature infants (Baylen *et al.*, 1975; Silverman *et al.*, 1974). The left atrial dimension is affected by other factors apart from the volume of blood reaching it. Decreased left ventricular compliance will result in an increase in left atrial dimension, as will lesions of the mitral valve (Hawley *et al.*, 1966; Yabek *et al.*, 1976). One patient (not in this series) had a ventricular septal defect and coarctation of the aorta, and was in left ventricular failure; he had a larger left atrial dimension than expected from the size of the shunt. A coexistent atrial septal defect would result in a left atrial dimension that was smaller than expected, and patients with this associated abnormality were excluded for this reason. Other echocardiographic features of right ventricular volume overload should enable one to diagnose atrial septal defect (Meyer *et al.*, 1972). The aortic root may be enlarged in other diseases such as Marfan's syndrome (Brown *et al.*, 1975), and may increase in size proportionally with the shunt in persistent ductus arteriosus. A dilated root would reduce the LAD/AR. In addition, we are assessing only the anteroposterior diameter of the left atrium. This dimension is closely correlated with the volume of the left atrium in a variety of conditions (Hirata *et al.*, 1969; Ten Cate *et al.*, 1974). Though in a recent analysis Yabek *et al.* (1976), stated that 'pancaking' of the left atrium was not seen with volume overload, it is possible that distortion of this axis of the left atrium might occasionally occur.

The recognition of these problems in any individual will enhance the usefulness of the technique. This totally non-invasive method of determining the size of the left-to-right shunt could then have many clinical applications.

One of the important considerations in the clinical evaluation of a shunt is its relative rather than its absolute magnitude. Large shunts should be distinguished from small shunts. The inaccuracies of the oximetric method make this an acceptable classification. A 'grey' zone around the 2:1 dividing line is appreciated. Fig. 4a shows that a left atrial dimension of 5 cm per m² BSA or less effectively divides small from large shunts. The one exception was an infant with clinical and radiographic evidence of a massive left-to-right shunt, who, despite the oximetric data, required immediate corrective surgery to relieve severe cardiac failure. Fig. 4b shows that an LAD/AR ratio of 1·6:1 or less forms an effective dividing line between large and small shunts. Of the 3 patients who had large left-to-right shunts by oximetry but small LAD/AR, 2 had small shunts radiographically and clinically. Thus echocardiography seems to be able to define shunt size with acceptable accuracy.

Another important application of this relation between shunt size and echocardiographic left atrial dimension is in the follow-up of the individual patient. Repeated echocardiographic estimations in an individual can be made accurately. This avoids the problem of variations within a group, and also in accurate standards. Repeated observations enable the physician to add an objective measurement to his clinical assessment. This previously would have required repeated catheterisation (Hoffman and Rudolph, 1965). A decrease in the size of the left-to-right shunt as reflected by a decrease in the left atrial dimension may be the result of closure of the ventricular septal defect, the development of pulmonary hypertension, or the development of infundibular pulmonary stenosis. A raised pulmonary arterial pressure can be detected on the echocardiogram (Nanda *et al.*, 1974; Hirschfeld *et al.*, 1975) and likewise, infundibular stenosis (Weyman *et al.*, 1975) and aneurysm formation (Sapire and Black, 1975) may have typical echocardiographic appearances.

Finally, another aspect of the study was the derivation of a regression equation from which shunt size can be estimated numerically. This has value in the individual, though the inaccuracies inherent in each method will be reflected in the number calculated (Kalmanson and Stegall, 1975).

A left-to-right shunt presents as a clinical composite. Echocardiography is a valuable procedure that adds to the total clinical evaluation of the situation. It does not localise the anatomical level of shunting within the ventricular septum or great arteries. Therefore, it does not supplant cardiac catheterisation in the investigation of these defects. It is, however, extremely valuable in providing an objective assessment of the magnitude of the left-to-right shunt. The need for repeated cardiac catheterisation can be avoided.

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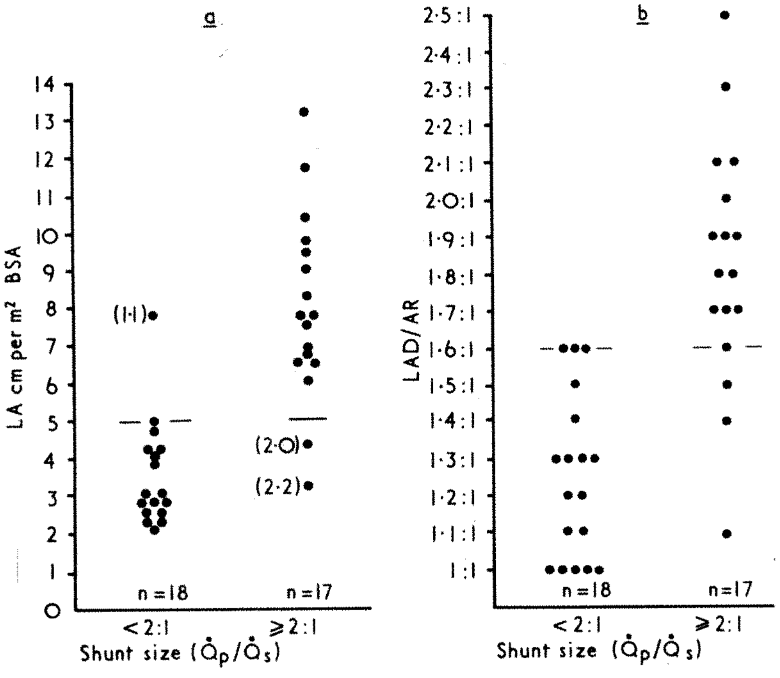

Fig. 4a and b *Results for patients with (≥2:1) and small (<2:1) shunts through a ventricular septal defect.*

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Echocardiographic diagnosis of primitive ventricle with two atrioventricular valves

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Anatomical studies have shown that the pathognomonic feature of primitive ventricle is absence of that portion of the interventricular septum which interposes between the atrioventricular valves. The relation of this posterior septum to the atrioventricular valves is such that echocardiography should be a particularly suitable technique for showing its presence or absence. When a posterior septum is present, it is seen on an echocardiogram as a double echo between the two atrioventricular valves. Its presence limits posterior movement of the septal cusp of the anterior atrioventricular valve. Absence of the posterior septum should, therefore, be seen echocardiographically as more than mere absence of the double septal echo. It should be possible to show unusual posterior excursion of the 'septal' cusp of the anterior atrioventricular valve and apposition of the 'septal' cusps of the atrioventricular valves during diastole. In most instances it should also be possible to demonstrate that the posterior great artery is in continuity with both atrioventricular valves. We have shown these echocardiographic features in 26 patients. The diagnosis of primitive ventricle has been confirmed at necropsy or at operation in 4 patients. In the other 22 patients the angiographic data are compatible with a diagnosis of primitive ventricle. Demonstration of these positive features at echocardiography is, therefore, of considerable value in the initial diagnosis of primitive ventricle and in particular its differentiation from other congenital malformations.

Surgical techniques for the correction of complicated congenital heart defects have been improving rapidly over the past decade. However, one anomaly that continues to pose problems, both in diagnosis and surgical correction, is the univentricular heart which we prefer to describe as primitive ventricle (Anderson *et al.*, 1976). Recently, there have been reports of successful correction, both by septation (Edie *et al.*, 1973; Maloney *et al.*, 1975) and by the use of valved conduits (Yacoub *et al.*, 1975). It has emerged from these reports that success or failure of surgical correction depends on an accurate preoperative knowledge of the anatomy. However, in our experience, this is a condition which can be difficult to diagnose, even after angiography. Absence of the posterior interventricular septum (the hallmark of primitive ventricle) can sometimes be difficult to demonstrate, while in other instances it is not possible to determine the number of atrioventricular valves present, both being features of considerable surgical importance. During an anatomical study currently in progress it became evident that echocardiography should be a suitable technique for establishing the diagnosis of primitive ventricle, since these hearts have more features amenable to echocardiographic identification than mere absence of the posterior septum. A specific study of morphology has therefore been undertaken to determine precise *positive* features of the anomaly that might be demonstrable using M-mode echocardiography. The clinical, angiographic, surgical, and necropsy data have then been correlated in patients with these echocardiographic features.

Materials and methods

(a) ANATOMICAL STUDY

Seventy-three hearts were studied in which there was absence of that part of the septum separating the atrioventricular valves. These hearts were compared with the normal. The specimens were taken

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from various cardiopathological collections, namely from Brompton Hospital, London; Royal Liverpool Children's Hospital; Southampton Western Hospital; Killingbeck Hospital, Leeds; The Hospital for Sick Children, London; and Grimsby General Hospital; University of Amsterdam; University of Leiden and Sint Antonius Ziekenhuis, Utrecht.

(b) ECHOCARDIOGRAPHIC STUDY

An M-mode echocardiogram was performed on 75 patients in whom a diagnosis of univentricular heart was suspected on clinical grounds. These included patients suspected of having atrioventricular valve atresia, which is in our opinion better considered as a type of univentricular heart, and other patients in whom the differential diagnosis was large ventricular septal defect or 'corrected transposition'. Recordings were made with a Smith-Kline Ekoline 20A echocardiograph interfaced with either a Honeywell fibreoptic strip chart recorder, or a Cambridge photographic strip chart recorder. A 2·25 MHz transducer was used in all patients other than neonates in whom a 5 MHz transducer was occasionally used. There were 26 patients whose echocardiograms showed the features which we considered to be diagnostic of primitive ventricle with two atrioventricular valves; these patients formed the basis of the study. The angiograms and catheterisation data of these patients were reviewed and compared with the echocardiographic findings. In those patients who subsequently had an operation or died, direct anatomical comparison was made.

Results

(a) ANATOMICAL CONSIDERATIONS

The common feature of the 73 hearts studied (Table) was complete absence of any posterior septal structure separating the septal cusps of the right and left atrioventricular valves (Fig. 1). In all the hearts the right and left valves closely resembled each other in terms of cusp pattern, each valve possessing a prominent 'septal' cusp (Fig. 2B). In all except one of the hearts studied, both of these 'septal' cusps were free to move into the outflow tract of the posterior great artery, this observation suggesting that during ventricular diastole during life the cusps would have been free to approximate each other in this posterior arterial outflow tract (Fig. 2A); in the other heart, both great arteries arose from an outlet chamber.

Though the ventricular inflow portions of all the hearts were identical, the hearts could be subdivided depending on the presence or absence of an anterior septal structure. Such a structure, smooth on its posterior aspect (Fig. 2B), was present in 59 hearts, dividing the ventricular segment of these hearts into a larger portion receiving the atrioventricular valves, the *primitive ventricle*, and a smaller portion which usually gave rise to a single great artery but did not contain atrioventricular valvar tension apparatus; we have termed this anterior chamber the *outlet chamber*. The septum separating the primitive ventricle from the outlet chamber was always situated anteriorly to both atrioventricular valves, though occasionally it was straddled by one of these valves. When straddling occurred (in 13 hearts), then some tension apparatus took origin from the outlet chamber. Though smooth on its posterior aspect, the septum was in no way comparable to the septum observed in the normal heart (Fig. 1 and 4). It never extended posteriorly to the crux of the heart, always tending to run to the margo acutus in primitive ventricular hearts (Fig. 2 and 3). Furthermore, in primitive ventricular hearts (Fig. 2 and 3) it never supported the septal cusp of the right atrioventricular valve, as it does in the normal heart (Fig. 4). In the primitive ventricles with outlet chamber, there was variation in the orientation of the anterior septum. In 28 hearts, the septum ran from a left anterior position in posterior direction to the margo acutus at the right border of the heart (Fig. 3): in these, the small trabeculated tail of the outlet chamber was also to the right. In 4 hearts the septum was directly in the frontal plane, placing the outlet chamber anterior to the primitive ventricle; in 3 of these the tail was left-sided and in one right-sided. In 27 hearts the septum ran from right anterior obliquely and posteriorly to the left margin of the heart, with the tail

Table *Details of 73 anatomical specimens studied*

Primitive ventricle with outlet chamber:			59
I	both valves entirely to main chamber	46	
	straddling right AV valve	8	
	straddling left AV valve	5	
II	outlet chamber to right	28	
	outlet chamber anterior	4	
	outlet chamber to left	27	
III	normal connections	10	
	l-transposition	27	
	d-transposition	16	
	double-outlet main chamber	3	
	double-outlet outlet chamber	1	
	single aortic trunk with pulmonary atresia	2	
Primitive ventricle without outlet chamber:			14
I	d-malposition ('normal relations')	5	
	d-malposition ('side-by-side')	4	
	l-malposition ('side-by-side')	5	

Note: These hearts were studied as part of an ongoing investigation; further details are to be published at a later date (Anderson, Wilkinson, and Becker, unpublished observations).

also to the left (Fig. 2). In the 13 hearts with a straddling valve, the outlet chamber was of larger dimensions and the septum was straddled by the anterior papillary muscle and anterior cusp of the valve. In 8 hearts the right atrioventricular valve straddled into a right-sided outlet chamber (Fig. 3). In 5 hearts the left-sided valve was the straddling valve, with the outlet chamber to the left in 4 and to the right in 1. Despite this straddling, the relation of the septal cusps of both atrioventricular valves to the posterior great artery was as in all the other primitive ventricular hearts (Fig. 3).

In the 14 hearts without an anterior septal structure dividing the ventricular cavity into main chamber and outlet chamber, a single ventricular chamber received both atrioventricular valves and supported both great arteries (except when one great artery was atretic). In terms of trabecular pattern, apart from the absence of the anterior septum, the hearts were identical with those which possessed outlet chambers. We have, therefore, termed these hearts *primitive ventricle without outlet chamber*. In 5 of these hearts the left part of the anterior septum fused with the infundibular septum to produce a well-formed infundibular chamber (Fig. 5). However, the septum did not extend apically to separate the infundibulum as part of a discrete outlet chamber.

In all the examples of primitive ventricle without outlet chamber, since the ventricle was a single chamber, the ventriculoarterial connection must by definition be one of double-outlet chamber. In primitive ventricle with outlet chamber, more variation was observed in ventriculoarterial connections (Table). In 10 hearts the arteries were normally connected; in 27 hearts l-transposition was present; in 16 d-transposition was observed; 3 hearts had double outlet main chamber, 1 heart possessed a double-outlet outlet chamber, and the remaining 2 hearts had single aortic trunks from the outlet chamber with pulmonary atresia. These variations in ventriculoarterial connection in no way affected the atrioventricular valves except to produce some alteration in the state of the ventriculoinfundibular fold. The posterior great artery arose from muscular tissue in only 8 of 73 hearts, and 6 of these had a double-outlet connection. In 9 hearts the posterior great artery was in fibrous continuity with only one atrioventricular valve, the right in 5 and the left in 4. In the remaining 56 hearts (77%) the posterior great artery was in fibrous continuity with both atrioventricular valves.

Thus, from this anatomical study we would expect that, in addition to absence of the posterior septum, other positive features of primitive ventricle would be identifiable echocardiographically.

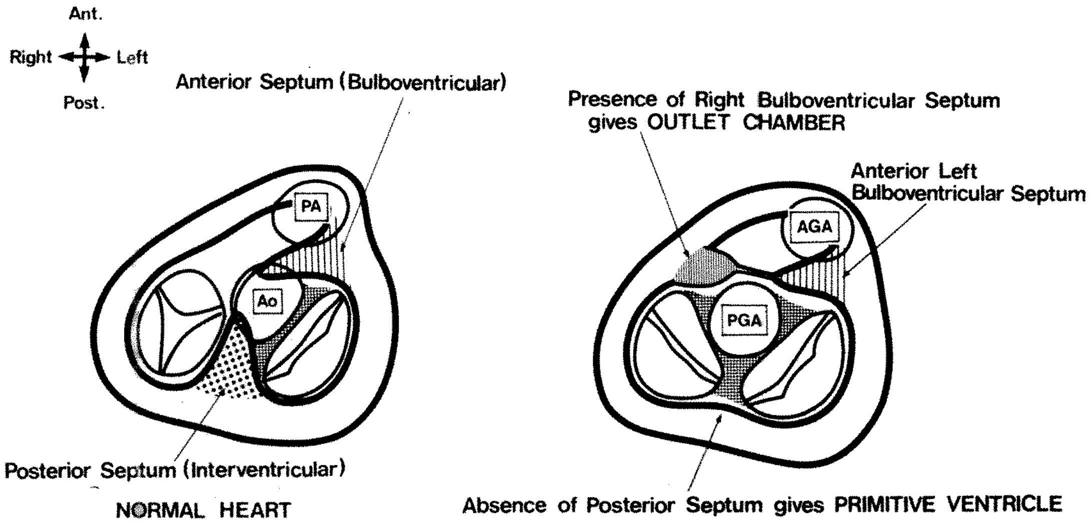
Ant.
Right
Left
Post.
Anterior Septum (Bulboventricular)
PA
Ao
Posterior Septum (Interventricular)
NORMAL HEART
Presence of Right Bulboventricular Septum gives OUTLET CHAMBER
Anterior Left Bulboventricular Septum
AGA
PGA
Absence of Posterior Septum gives PRIMITIVE VENTRICLE

Fig. 1 *Cross-sectional diagrams comparing the septal components of the normal heart (left hand diagram) with primitive ventricle (right hand diagram). In the normal heart the muscular septum has two components; an anterior, bulboventricular septum between the infundibulum and the left ventricle and a posterior, interventricular component between the atrioventricular valves. Absence of this posterior septal component gives the univentricular heart, termed by us 'primitive ventricle'. If the anterior bulboventricular septum persists in its entirety, then the primitive ventricle will be associated with an outlet chamber. Should the right portion of the bulboventricular septum be absent, then primitive (single or common) ventricle without outlet chamber will result.*

These are (a) free 'septal' excursion of the right atrioventricular valve; (b) apposition of the 'septal' valve cusps in ventricular diastole, and (c) in the majority of hearts continuity of the posterior great artery with both atrioventricular valves (Fig. 6).

(b) ECHOCARDIOGRAPHIC DATA

Between January 1975 and March 1976, 75 patients in whom a diagnosis of primitive ventricle was either suspected or considered as a differential diagnosis, underwent echocardiographic study at the Brompton Hospital. Of these patients 26 fulfilled the expected criteria for primitive ventricle with two atrioventricular valves. All 26 patients showed (a) absence of a posterior interventricular septum between the two atrioventricular valves, (b) unusual posterior excursion of the posterior cusp of the anterior atrioventricular valve which closely resembled the posterior atrioventricular valve, and (c) apposition of the 'septal' cusps of the two atrioventricular valves during diastole (Fig. 7). In 25 patients there was echocardiographic 'continuity' between the two atrioventricular valves and the posterior semilunar valve (Fig. 8 and 9). An anterior (anatomically bulboventricular) septum was found with certainty in only 7 patients.

The diagnosis of primitive ventricle with or without outlet chamber was confirmed at operation or necropsy in 4 patients. Three of these patients had been diagnosed angiographically as primitive

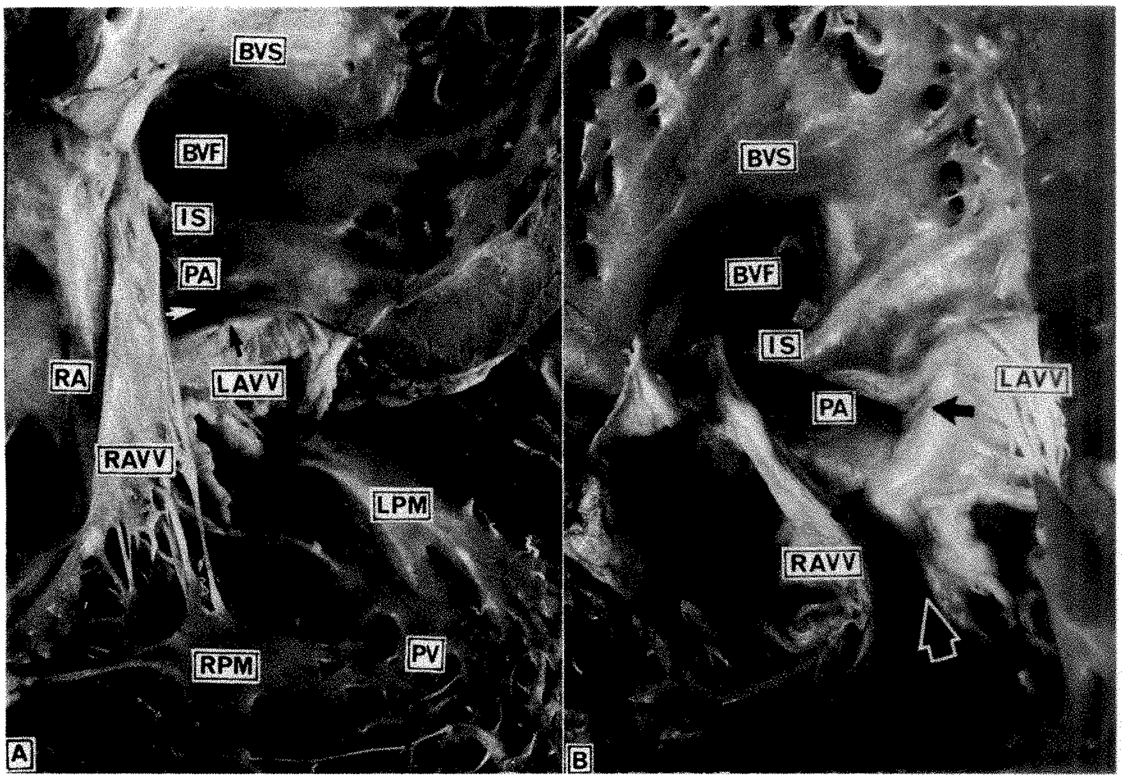

Fig. 2 *(A) Photograph of the primitive ventricle from a specimen of primitive ventricle with outlet chamber. The heart has been opened by a frontal cut through the primitive ventricle (PV), which receives both atrioventricular valves (RAVV, LAVV), and the anterior aspect has been reflected superiorly so that the bulboventricular septum (BVS) and the bulboventricular foramen (BVF) are seen in the top of the picture. Through the bulboventricular foramen part of the outlet chamber can be seen. The infundibular septum (IS) separates the pulmonary artery (PA) from the aorta which arises from the outlet chamber. Note that both atrioventricular valves are free to move into the outflow tract of the posterior great artery (arrows). LPM, left-sided papillary muscle; RPM, right-sided papillary muscle; RA, right atrium. (B) Another view of the same heart, with retraction of the 'septal' cusp of the right atrioventricular valve. The absence of the posterior septum is now evident (large arrow) and the potential for free movement of both atrioventricular valves into the outflow tract of the posterior artery is clearly seen (small arrows).*

ventricle. The fourth patient had been diagnosed angiographically as double-outlet right ventricle, but the echocardiogram (Fig. 9) showed the features of primitive ventricle, and at operation this latter diagnosis was confirmed.

Of the remaining 22 patients, 16 had originally been diagnosed as primitive ventricle with or without outlet chamber. Four had been diagnosed as 'corrected transposition' (the combination of transposition and atrioventricular discordance). In 2 further patients the differential diagnosis was between transposition with ventricular septal defect and a primitive ventricle, and 2 had been given no definite diagnosis. As a result of our anatomical study, we were able to review the angiograms with the morphological features of primitive ventricle in mind, and look for the specific diagnostic features. Thus, an angiographic diagnosis of primitive ventricle was made if there was definite evidence of 2 atrioventricular valves entering the same ventricular chamber. The relation of the posterior great artery to the main chamber was particularly helpful in this respect, since in primitive ventricle the artery arises from the mid-point of the chamber, being contiguous with both atrioventricular valves. In the presence of a posterior septum, the origin of the posterior great artery is eccentric. We also felt that we were able to distinguish between an outlet chamber and a morphologically right ventricle on angiographic appearances, the former being smaller, possessing less of an apical trabeculated segment, and never receiving the entirety of an atrioventricular valve. Using these criteria the angiograms were found to be compatible with a diagnosis of primitive ventricle in all these 22 patients.

The angiograms showed an outlet chamber in 13 patients; in only 7 (54%) of these was an anterior septum detected echocardiographically. However, in no case was an anterior septum shown on the echocardiogram, where an outlet chamber was not

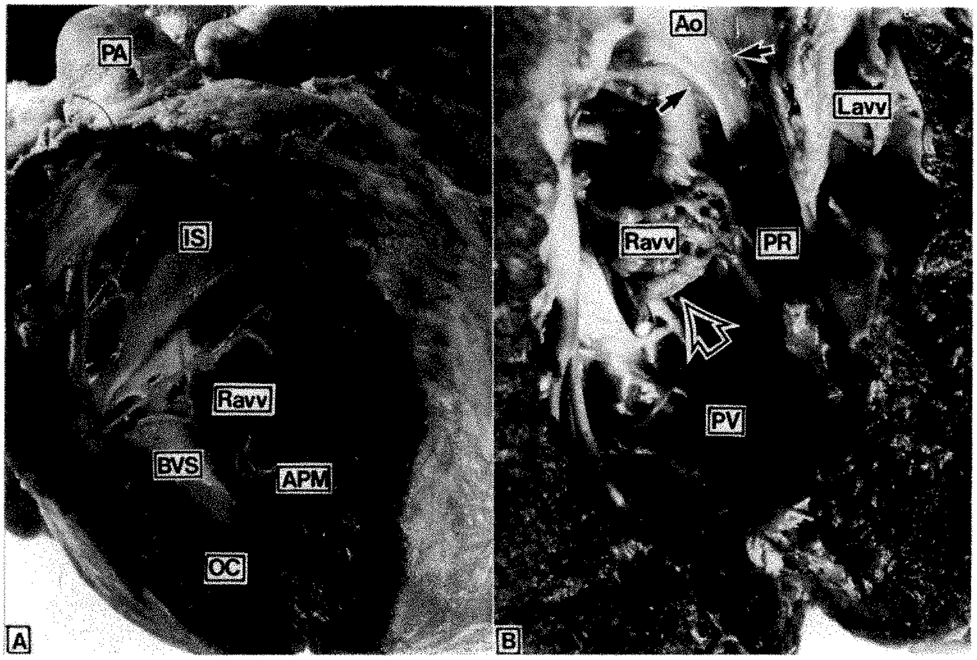

Fig. 3 *Photographs of an example of primitive ventricle with outlet chamber and straddling right atrioventricular valve. Fig. 3A is a view of the outlet chamber (OC), which supports the normally connected pulmonary artery (PA). Note that the anterior bulboventricular septum (BVS) runs from left anterior in posterior direction to the right acute margin of the heart where it fuses with the infundibular septum (IS). It is straddled by the anterior papillary muscle (APM) of the right AV valve (Ravv). Fig. 3B shows the primitive ventricle (PV), which receives the entirety of the left atrioventricular valve (Lavv) and the greater part of the right valve. Note that the 'septal' cusp of the right valve is tethered into the primitive ventricle, and that both cusps are free to move into the aortic outflow tract (small arrows) where they are in fibrous continuity with the aortic valve. Note that the septum (large arrow) runs to the acute margin of the ventricle and does not interpose between the atrioventricular valves. In the anticipated site of the posterior septum a well-formed posterior ridge (PR) is present.*

present on the angiogram. One patient was found at necropsy to have a straddling right atrioventricular valve; this was not apparent on either the echocardiogram or the angiogram. The angiograms of one other patient also suggested a straddling right atrioventricular valve, but this was not shown on the echocardiogram.

Discussion

Previous echocardiographic studies have shown that absence of septal echoes may indicate presence of a single (primitive) ventricle (Chesler *et al.*, 1971; Meyer and Kaplan, 1973; Assad-Morrell *et al.*, 1974; Ferrer *et al.*, 1975; Felner *et al.*, 1976; Seward *et al.*, 1976). However, since it is possible to miss septal echoes in a heart containing a septum the condition may be incorrectly diagnosed. Our study has shown that there are positive features of the primitive ventricle that can be seen in addition to absence of the septum, so that echocardiographic diagnosis can be based on positive rather than negative findings. Our anatomical study confirmed that the cardinal feature of the primitive ventricle is absence of the posterior portion of the interventricular septum (Van Praagh *et al.*, 1964; Lev *et al.*, 1969). It also showed that absence of this septum affects the movements of the atrioventricular valves in such a way as to give a characteristic echocardiographic pattern, namely: (a) unusual posterior excursion of the posterior cusp of the anterior atrioventricular valve so that it closely resembles the posterior valve, (b) apposition of the septal cusps of the two atrioventricular valves, and (c) in the majority of cases echocardiographic continuity between the posterior semilunar valve and the two atrioventricular valves. Thus, if diagnosis is based on these findings, false positive diagnoses should be prevented (should it merely have not proved possible to echo a normally positioned posterior septum), and false negatives should be avoided in the circumstance of large conjoined papillary muscles giving the angiographic appearance of a posterior septum. The finding of continuity of the posterior great artery with both atrioventricular valves is perhaps more difficult to establish than the other criteria. Furthermore, since absolute continuity of adjacent fibrous structures is difficult to establish echocardiographically, it may seem of less value. None the less, Seward *et al.* (1976) showed echocardiographic continuity of the posterior great artery with the posterior atrioventricular valve in 27 of 31 patients, while Felner *et al.* (1976) observed this feature in 5 of 6 patients. Since anatomical continuity of the posterior great artery with both atrioventricular valves was seen in 77 per cent of our necropsy specimens, with continuity of one valve and contiguity of the other in a further 14·5 per cent, we believe the finding to be of considerable significance if the term *contiguity* is used rather than continuity. Thus, there are very few other congenital anomalies apart from primitive ventricle which would present the feature of both atrioventricular valves in contiguity with the posterior great artery in the absence of a posterior septum.

In our study the echocardiograms of 26 patients showed these anticipated features of single ventricle with two atrioventricular valves. The correlation

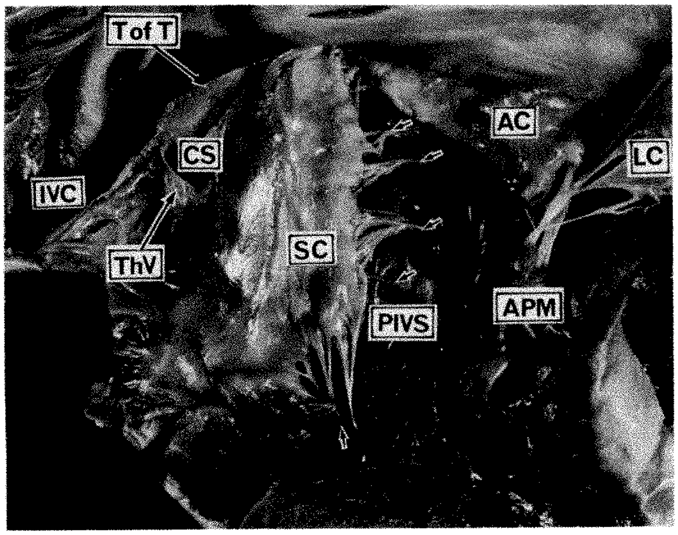

Fig. 4 *Photograph of a normal heart opened through the posterior aspect of the right atrioventricular orifice with reflection of the parietal wall. Note how the septal cusp (SC) of the tricuspid valve is tethered tightly to the posterior interventricular septum (PIVS) by multiple, small chordae and papillary muscles (arrowed). The anterior (AC) and lateral (LC) cusps are tethered by the prominent anterior papillary muscle (APM). The inferior vena cava (IVC), Thebesian valve (ThV) guarding the coronary sinus (CS) and the site of the tendon of Todaro (T of T) are all visible within the right atrium.*

with angiographic, surgical, and necropsy date was good. Our attempts to identify an anterior septum and its relation to the anterior atrioventricular valve have not been entirely successful. Others have achieved greater success in this respect, and C. Mortera, S. J. Hunter, and M. J. Tynan (1976, personal communication) have positively identified outlet chambers by echocardiography in over 90 per cent of patients shown by cardiac catheterisation to have primitive ventricle with outlet chamber. An anterior septum straddled by the right atrioventricular valve has also been identified echocardiographically, by Seward *et al.* (1975a) and by Lacorte *et al.* (1976); examination of the illustrated echocardiograms from both these reports shows that they fulfil the criteria we have suggested for primitive ventricle. It is our belief that these hearts are similar to the hearts we studied and characterised as primitive ventricle with outlet chamber and straddling atrioventricular valves. It can logically be argued that if part of an atrioventricular valve enters an anterior chamber this can no longer be considered an outlet chamber. In these circumstances, as suggested by Liberthson *et al.* (1971), the chambers can alternatively be designated as primitive left and primitive right ventricles. Be that as it may, there is no doubt in our minds that the septum straddled in such hearts is the bulboventricular septum as in primitive ventricle with outlet chamber rather than the interventricular septum as in the normal heart; furthermore, the anterior chamber resembles an outlet chamber rather than a right ventricle.

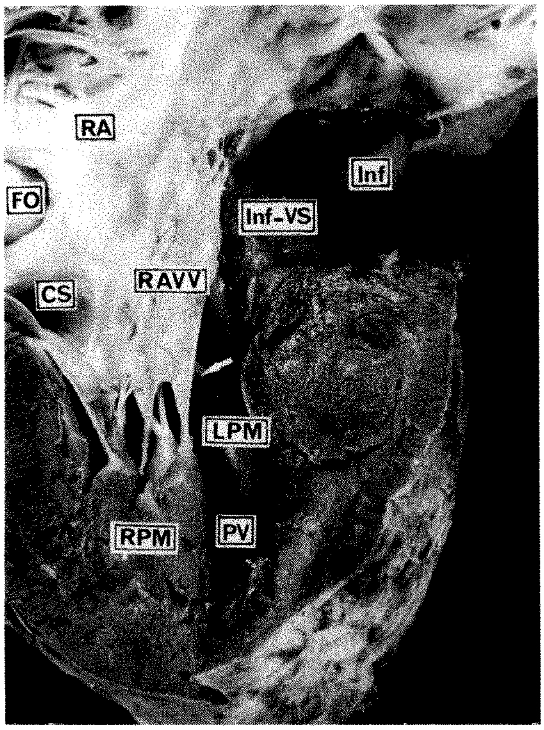

Fig. 5 *Photograph of a specimen of primitive ventricle without outlet chamber, opened through a posterior cut in the right atrioventricular orifice (exactly as in Fig. 2). Though an infundibulo-ventricular septum (Inf-VS) separates the infundibulum (Inf) from that part of the heart receiving the atrioventricular valves, this septum does not continue to the right and an outlet chamber is not present. The great arteries are normally connected. Again note the absence of the posterior septum (arrowed) between the right atrioventricular valve (RAVV) with its papillary muscles (RPM) and the papillary muscle (LPM) of the left atrioventricular valve. PV, primitive ventricle; CS, coronary sinus; FO, foramen ovale; RA, right atrium.*

An additional technique which may be of value in the investigation of primitive ventricle is contrast echocardiography. Using such contrast echocardiography the Mayo Clinic group have had considerable success in diagnosis (Seward *et al.*, 1975b; J. B. Seward, 1976, personal communication). This technique should also be of value in distinguishing patients with straddling atrioventricular valves.

We thus believe that a positive diagnosis of primitive ventricle can be made echocardiographically. This is of importance since it allows the differentiation of primitive ventricle from other conditions with which it may be confused angiographically. The most significant of these is congenitally corrected transposition (transposition with atrioventricular discordance). Indeed some authors contend that primitive ventricle with left-sided outlet chamber should be considered as a variant of 'corrected transposition' (Friedberg and Nadas, 1970). We agree with Ruttenberg (1970) and believe that the two should be considered as separate anomalies, the presence or absence of a posterior septum being the distinguishing feature. This is equally true of the distinction of primitive ventricle with straddling left atrioventricular valve from corrected transposition. As we have shown, the absence of the posterior septum is particularly well demonstrated echocardiographically, while it also appears that congenitally corrected transposition itself has clearly recognisable echocardiographic features (Beardshaw *et al.*, 1976; Rey and Lablanche, 1976; Keutel and Hagenmuller, 1976).

Finally, it must not be presumed that the echocardiogram provides all the answers. We believe that cardiac catheterisation is essential in the study of all suspected cases of primitive ventricle. This is par-

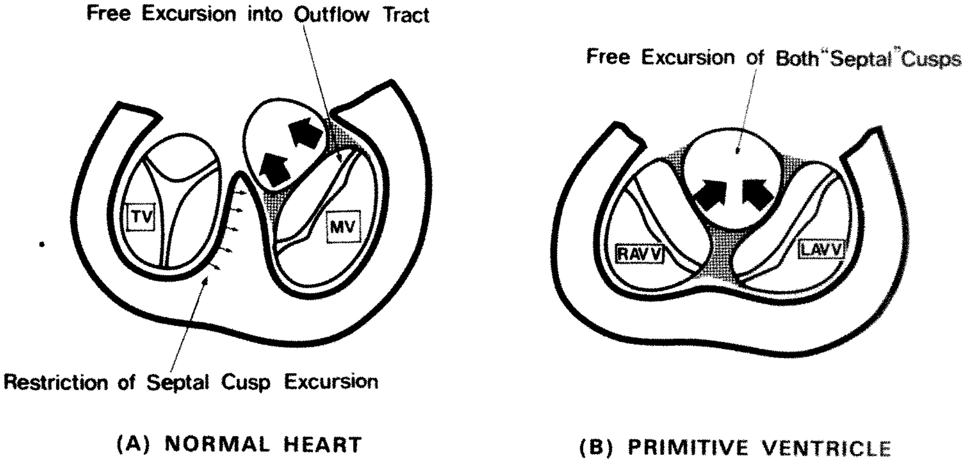
Free Excursion into Outflow Tract
Free Excursion of Both "Septal" Cusps
TV
MV
RAVV
LAVV
Restriction of Septal Cusp Excursion
(A) NORMAL HEART
(B) PRIMITIVE VENTRICLE

Fig. 6 *Diagrams showing how the anatomy illustrated in Figures 2 to 4 affects the valve movements in (A) the normal heart and (B) primitive ventricle. Orientation as indicated in Fig. 1. TV, tricuspid valve; MV, mitral valve. Note that the morphology of the two atrioventricular valves is similar in primitive ventricle, and that they are therefore designated right (RAVV) and left (LAVV).*

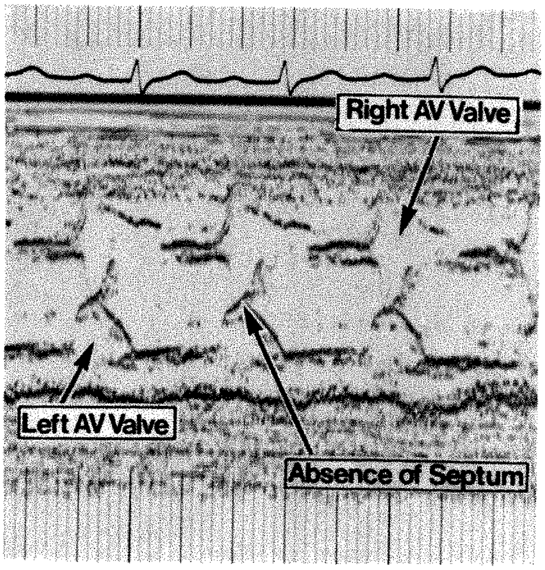

Fig. 7 *Echocardiogram of primitive ventricle. Note (a) the unusual posterior excursion of the right atrioventricular valve which resembles the left atrioventricular valve, (b) the meeting of the atrioventricular valves during diastole, and (c) the absence of echoes from the posterior interventricular septum.*

ticularly so in order to show the presence or absence of an outlet chamber, a feature which in our hands has not so far lent itself to reliable echocardiographic delineation. In planning treatment, the presence of associated lesions, including semilunar valve stenosis, must also be established; these are also more clearly shown by conventional haemodynamic study and angiography. At the time of angiography it should also be possible to perform contrast echocardiography which, as the Mayo Clinic group have shown, gives considerably more information (Seward *et al.*, 1975b). Using the combined techniques of echocardiography and angiography, we believe it should be possible to diagnose single ventricle accurately and provide information on the presence or absence of an outlet chamber and the number and condition of atrioventricular valves present, essential information for any subsequent operation.

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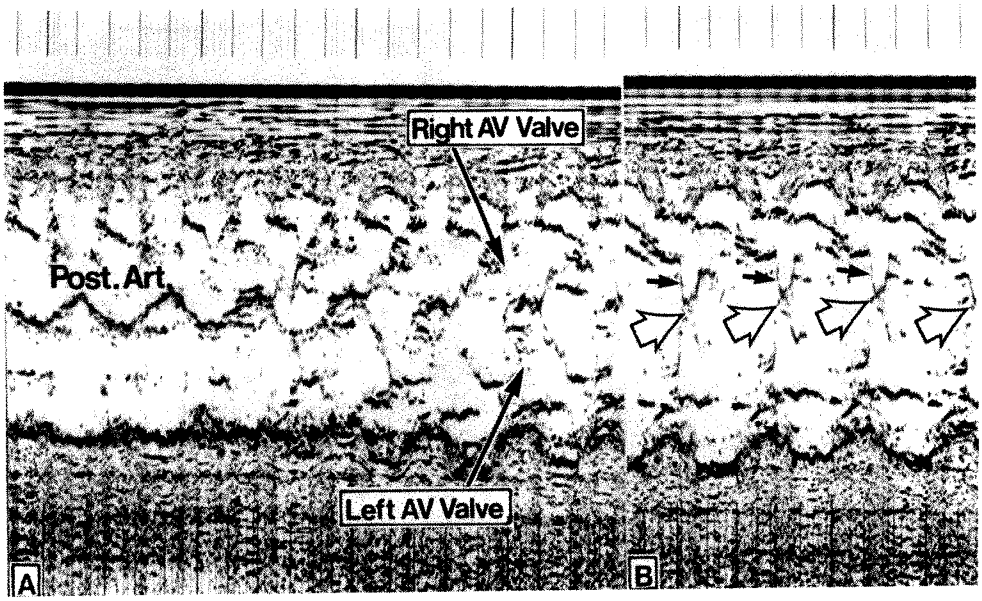

Fig. 8 *(A) Echocardiogram of primitive ventricle showing a scan from the posterior artery into the right and left atrioventricular (AV) valves. There is contiguity between these structures. (B) Scan of the valves themselves illustrates meeting of the 'septal' cusps in diastole in absence of a septum (open arrows) and unusual posterior excursion of the right valve (closed arrows) so that it resembles the left valve.*

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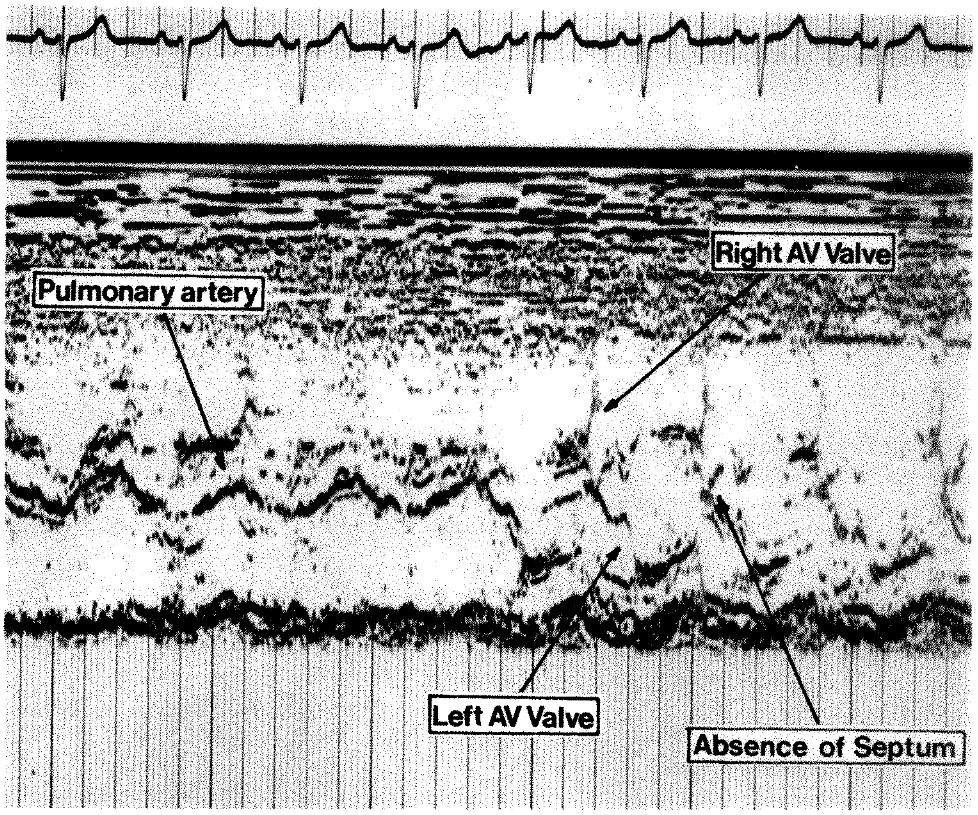

Fig. 9 *Echocardiographic scan of a patient with primitive ventricle. Note that the posterior great artery (known to be the pulmonary artery) is in contiguity with both atrioventricular valves, though the echoes from valve to valve are not actually continuous, and that the other criteria for primitive ventricle are also present (compare with Fig. 7 and 8). This patient was diagnosed angiographically as double-outlet right ventricle, but primitive ventricle without outlet chamber was confirmed at operation.*

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British Heart Journal, 1977, **39**, 276-288

Natural history of the ventricular septal defect in tricuspid atresia and its surgical implications[1]

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We have previously reported isolated cases of anatomical and functional closure of ventricular septal defects in tricuspid atresia. To study this phenomenon further, clinical, angiographic, and pathological findings in 20 consecutive cases of tricuspid atresia were reviewed. Sixteen cases were found to have normally related great arteries (type I) and 4 had transposition (type II). In 6 of these patients there was evidence of closure of a ventricular septal defect; in 3 this was complete and in the other 3, partial. Five of these ventricular septal defect closures occurred in type I patients and one among type II. Increasing cyanosis and polycythaemia and/or disappearance of a previously heard murmur were observed in all patients; these signs are more conspicuous in complete closure than in partial.

The incidence of closure of ventricular septal defect in tricuspid atresia is 38 per cent and approximates to the incidence of spontaneous closure of isolated ventricular septal defects. Progressive muscular 'encroachment' of the margins of ventricular septal defects with subsequent fibrosis and covering by endocardial proliferation is the most likely mechanism of closure in tricuspid atresia. The factors initiating the closure of ventricular septal defect remain unknown, but because of its occurrence in patients both with and without previous shunt operations, it is reasonable to assume that closure of ventricular septal defect in tricuspid atresia is not initiated or accelerated by these surgical shunts.

Recent developments in surgical technique permit total surgical correction of tricuspid atresia at least in a physiological sense, but these operations can be successfully performed only in older children (over 8 years). Thus, palliation is essential in younger patients until they reach the age for total correction. A Blalock-Taussig shunt is recommended in preference to a Glenn anastomosis because the latter may leave the left pulmonary circuit without blood supply if the ventricular septal defect closes. In type II cases, a large and non-restrictive ventricular septal defect is essential for survival of the patient after the Fontan operation. For this reason, the size of the ventricular septal defect should be evaluated before and at the time of surgical correction. If the ventricular septal defect is small in a type II case, resection of the ventricular septum or a complete bypass of the ventricular septal defect and right ventricle is necessary at the time of the Fontan operation.

Spontaneous closure of isolated ventricular septal defects is well known (Azevedo *et al.*, 1958; Evans *et al.*, 1960; Nadas *et al.*, 1961; Arcilla *et al.*, 1963; Bloomfield, 1964; Hoffman and Rudolph, 1965). In simple ventricular septal defect this is clearly beneficial to the patient. In some complex cardiac lesions, however, an open ventricular septal defect is necessary to maintain adequate intracardiac shunting essential for survival of the patient; these have been named 'physiologically advantageous ventricular septal defects' (Rao and Sissman, 1971; Rao *et al.*, 1974). Spontaneous closure of defects of this type is rare but does occur. We have previously reported isolated cases of spontaneous anatomical and intermittent functional closure of the ventricular septal defects in tricuspid atresia (Rao and Sissman, 1971; Rao *et al.*, 1974). To study this phenomenon further clinical, angiographic, and pathological findings in 20 consecutive cases of tricuspid atresia seen at the Medical College of Georgia were reviewed. The purpose of this paper is to report these observations to assess the incidence of ventricular

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septal defect closure in tricuspid atresia, to review the anatomical and physiological consequences of such closure, to discuss the mechanism of closure, and to comment on the therapeutic implications of closure of the ventricular septal defect in tricuspid atresia.

Subjects, methods, and results

The clinical, catheterisation and angiographic, and necropsy findings in all cases of tricuspid atresia seen at the Medical College of Georgia between 1966 and 1974 were reviewed. The commonly accepted criteria were used for diagnosis and inclusion in this study (Gasul *et al.*, 1966; Keith *et al.*, 1967; Diehl *et al.*, 1968; Nadas and Fyler, 1972). Twenty consecutive cases seen over the 8-year period (1966 to 1974) form the basis of this study. The diagnosis of tricuspid atresia was made by catheterisation and angiography in 11 patients, by catheterisation, angiography, and necropsy in 8, and by clinical findings alone in 1. Nine infants presented with symptoms during the first month of life, 8 between 1 month and 1 year, and the remaining 3 between the ages of 1 and 2 years. Their ages at the time of death or last clinical examination varied from 4 days to 16 years, with a mean age of 5 years and a median age of 7 months. The sex distribution was 1·5:1 male-to-female and is consistent with the slight preponderance of males reported for this lesion (Neill and Brink, 1955; Taussig *et al.*, 1973; Dick *et al.*, 1975). These cases were grouped according to the modified Keith classification (Edwards and Burchell, 1949; Keith *et al.*, 1967). Sixteen cases were classified as type I and four as type II, and further subgrouping is shown in Table 1. The relative frequency of these types is similar to that in other series (Keith *et al.*, 1967; Diehl *et al.*, 1968; Nadas and Fyler, 1972). One case with normally related great arteries had a large ventricular septal defect and pulmonary atresia and cannot be classified with the currently available classifications (Keith *et al.*, 1967; Diehl *et al.*, 1968); it is suggested that cases of this variant should be classified as type ID. Additional cardiac anomalies were present in 13 patients (Table 2); these are not dissimilar to those in other series except that the aortic arch anomalies reported in type II by Marcano *et al.* (1969) were not seen in any type II patient in this series.

Table 1 *Classification of tricuspid atresia patients seen at the medical college of Georgia (1966-74)*

	Type I	*Type II*
A	4	—
B	9	2
C	2	2
D	1	—

Of 20 cases reviewed, 6 had clinical, angiographic, or pathological evidence for closure of ventricular septal defect. Three patients had complete closure and 3 partial. Each of these cases will be presented briefly.

Case reports

CASE 1

A 4-week-old female infant with cyanosis and a pansystolic murmur was found at cardiac catheterisation (Table 3) and selective cineangiography to have tricuspid atresia with normally related great arteries and a moderate-sized ventricular septal defect (Fig. 1). The haematocrit was 57 per cent. Re-examination at 6 weeks and 3 months of age showed increased cyanosis and polycythaemia (haematocrit 63%). The previously heard pansystolic murmur was still present. The chest *x*-ray showed diminished pulmonary vascular markings compared with the earlier film. At 5 months of age a grade 2/6 ejection murmur was heard and at 6 months the murmur was only grade 1/6. The haematocrit had risen to 71 per cent. An aortopulmonary shunt (Waterston) was performed, and the infant appeared to improve, but two days later had a cardiac arrest and died.

At necropsy, the diagnosis of tricuspid atresia without transposition was confirmed. A patent foramen ovale and an ostium primum atrial septal defect were present. There was an endothelialised recess in the left ventricular aspect of the ventricular septum (Fig. 2A): this appeared to end blindly, but with little force a probe could be passed through to the right ventricle; with a light source on the left

Table 2 *Additional cardiac defects in 13 of the 20 cases of tricuspid atresia*

Persistent ductus arteriosus	5
Persistent left superior vena cava	4
Right aortic arch	2
Hypoplastic ascending aorta	1
Coarctation of aorta	1
Subaortic stenosis	1
Absent left pulmonary artery	1
Total anomalous pulmonary venous connection	1
Obstructed patent foramen ovale	1
Total	17*

*More than one associated lesion was present in some cases.

ventricular side, a ventricular septal defect opening into the right ventricular cavity was seen after removal of the probe (Fig. 2B). It is believed that the defect was in fact completely closed, but that the probe ruptured the thin endothelial membrane closing a small ventricular septal defect. There was no valvar or infundibular pulmonary stenosis. The ascending aorta-to-right pulmonary artery anastomosis was patent.

CASE 2

The second patient was first seen at the Medical College of Georgia at the age of 22 months because of cyanosis. A pansystolic murmur was recorded. Right atrial angiography suggested a diagnosis of tricuspid atresia with atrial and ventricular septal defects and without transposition. A Glenn procedure was performed and the cyanosis improved. He was first seen by our paediatric cardiology group at

Table 3 *Cardiac catheterisation data*

	SVC	*IVC*	*RA*	*PV*	*LA*	*LV*	*Ao*	*PA*	*RV*
Case 1—1 month									
Oxygen saturation (%)	62	—	69	—	89	92	—	—	—
Pressure (mmHg)	—	—	—	—	—	110/6	—	—	—
Case 2—12 years									
Oxygen saturation (%)	65	72	70	—	80	84	—	RPA 67*	—
Pressure (mmHg)	mean = 10	—	a = 11 v = 7 mean = 6	—	a = 10 v = 7 mean = 6	116/7	—	mean = 10*	—
Case 3—3 days									
Oxygen saturation (%)	—	—	28	—	31	34	—	—	—
Pressure (mmHg)	—	—	a = 15 v = 7 mean = 9	—	a = 11 v = 8 mean = 8	76/8	—	—	—
Case 3—10 months									
Oxygen saturation (%)	86	62	84	—	82	80	—	—	—
Pressure (mmHg)	—	—	a = 22 v = 16 mean = 14	—	a = 22 v = 18 mean = 14	100/10	—	—	—
Case 4—6 weeks									
Oxygen saturation (%)	45	—	51	99	87	88	87	—	—
Pressure (mmHg)	—	—	a = 20 v = 7 mean = 8	—	a = 12 v = 10 mean = 6	82/5	80/45 mean = 60	—	—
Case 4—4 months									
Oxygen saturation (%)	53	57	56	—	80	82	—	—	—
Pressure (mmHg)	—	—	a = 14 v = 5 mean = 7	—	a = 5 v = 7 mean = 4	83/3	—	—	—
Case 4—after balloon septostomy									
Pressure (mmHg)			a = 10 v = 3 mean = 4		a = 7 v = 8 mean = 2				
Case 5—16 years									
Oxygen saturation (%)	60	—	60	98	83	83	83	RPA 64*	—
Pressure (mmHg)	mean = 10	—	a = 13 v = 8 mean = 10	—	a = 11 v = 8 mean = 7	115/10	115/60 mean = 75	mean = 10*	—
Case 6—5 years									
Oxygen saturation (%)	52	—	54	—	86	85	—	—	—
Pressure (mmHg)	—	—	v = 14 a = 12 mean = 12	—	a = 11 v = 11 mean = 9	114/9	—	—	—
Case 6—14 years									
Oxygen saturation (%)	68	67	68	97	84	84	84	84	84
Pressure (mmHg)	—	—	a = 12 v = 11 mean = 10	—	a = 12 v = 11 mean = 10	140/10	140/80 (100/80)†	28/14‡ 120/20§	140/15

*RPA entered via Glenn anastomosis.
†Descending aorta distal to coarctation.
‡Pulmonary artery distal to band.
§Pulmonary artery proximal to band.
Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium RV, right ventricle, SVC, superior vena cava.

the age of 12 years because of moderate exercise intolerance, increased cyanosis, and headaches. He then had a single second sound and a grade 2/6 ejection murmur at the left sternal border. Chest *x*-rays showed a normal sized heart and finely reticular pulmonary vascular markings. The electrocardiogram showed right atrial enlargement and left ventricular hypertrophy, with a mean frontal plane vector of −60° and a counterclockwise loop. His haematocrit was 75 per cent. Cardiac catheterisation (Table 3) and selective cineangiography confirmed the diagnosis of type I tricuspid atresia, and showed a patent Glenn shunt. Left ventricular angiography showed no ventricular septal defect. The left pulmonary circuit appeared to fill by enlarged collateral vessels and the right by the Glenn shunt. A left subclavian-pulmonary artery anastomosis (Blalock-Taussig) was performed without incident. He improved clinically and the haematocrit dropped to 54 per cent. A repeat catheterisation with angiography at 15 years again confirmed closure of the ventricular septal defect. Both the Glenn and Blalock-Taussig shunts were functioning. The patient is now awaiting a Fontan operation.

CASE 3

This male infant presented with cyanosis on the third day of life. Pertinent findings on examination included conspicuous cyanosis and a grade 2/6 systolic murmur at the left lower sternal border. Chest *x*-rays showed minimal cardiomegaly and decreased pulmonary vascular markings. The electrocardiogram showed right atrial enlargement, a mean frontal plane vector of −30°, and left ventricular hypertrophy. Cardiac catheterisation (Table 3) and cineangiography showed tricuspid atresia with normally related great arteries. Selective left ventricular angiography demonstrated a very small crescent-like right ventricle opacified via a small ventricular septal defect (Fig. 3 A). There was very severe systemic arterial desaturation, and an emergency ascending aorta-to-right pulmonary artery (Waterston) anastomosis was performed. The infant improved, but two weeks later developed congestive heart failure, which was controlled medically. He was re-examined at 1, 3, 6, and 10 months of age, and had a continuous murmur of the aortopulmonary anastomosis. The ventricular septal defect murmur was no longer heard. Though the cardiac failure was controlled, there were persistent cardiomegaly and increased pulmonary vascular markings. A repeat cardiac catheterisation (Table 3) and angiography at 1 year of age showed tricuspid atresia, with a well-functioning aortopulmonary shunt (Fig. 3 C). On left ventricular angiograms in the posteroanterior and left anterior oblique projections there was no evidence of the ventricular

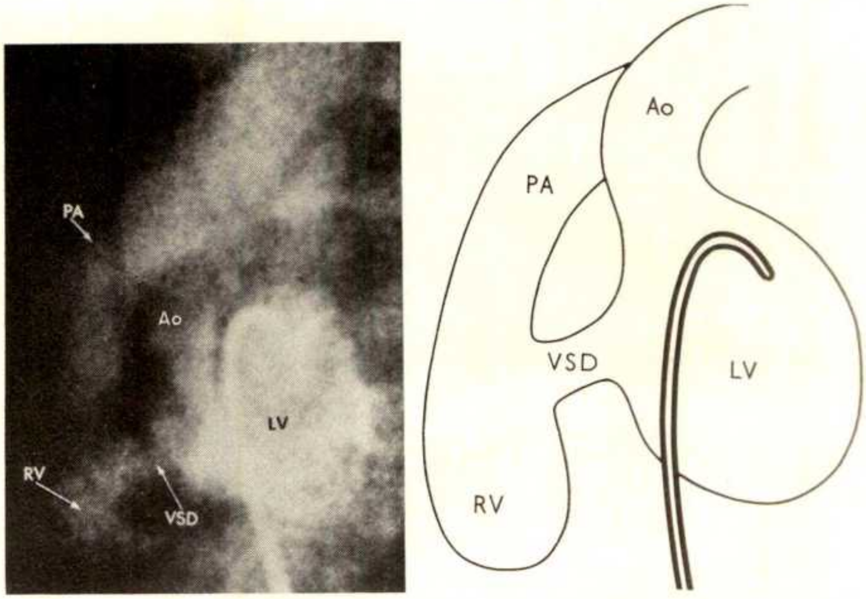


Fig. 1 *Case 1. Selected frame from left ventricular cineangiogram (left anterior oblique view) showing opacification of the right ventricle (RV) via ventricular septal defect (VSD). LV, left ventricle; PA, pulmonary artery.*

septal defect (Fig. 3 B and C). Total anomalous pulmonary venous connection was seen then and on reinvestigation at the age of 4 years. This patient is now undergoing staged correction of the anomalous pulmonary venous return and tricuspid atresia.

CASE 4

This female infant presented with tachypnoea, intermittent cyanosis, and failure to thrive at 6 weeks of age. She then weighed less than at birth and was slightly cyanosed; there were signs of moderate congestive heart failure. The praecordium was hyperdynamic, and there was a grade 4/6 pansystolic murmur with thrill at the left lower sternal border; the second heart sound was widely split with prominent pulmonary component and there was a loud apical third heart sound. The electrocardiogram showed a mean frontal plane vector of −40° and left ventricular hypertrophy. Chest *x*-ray showed considerable cardiomegaly and pulmonary plethora. The haematocrit was 52 per cent. The infant was admitted to hospital for treatment of heart failure. Cardiac catheterisation (Table 3) and selective cineangiography 3 days later showed type I tricuspid atresia, patent foramen ovale, and a large ventricular septal defect. Aortogram excluded

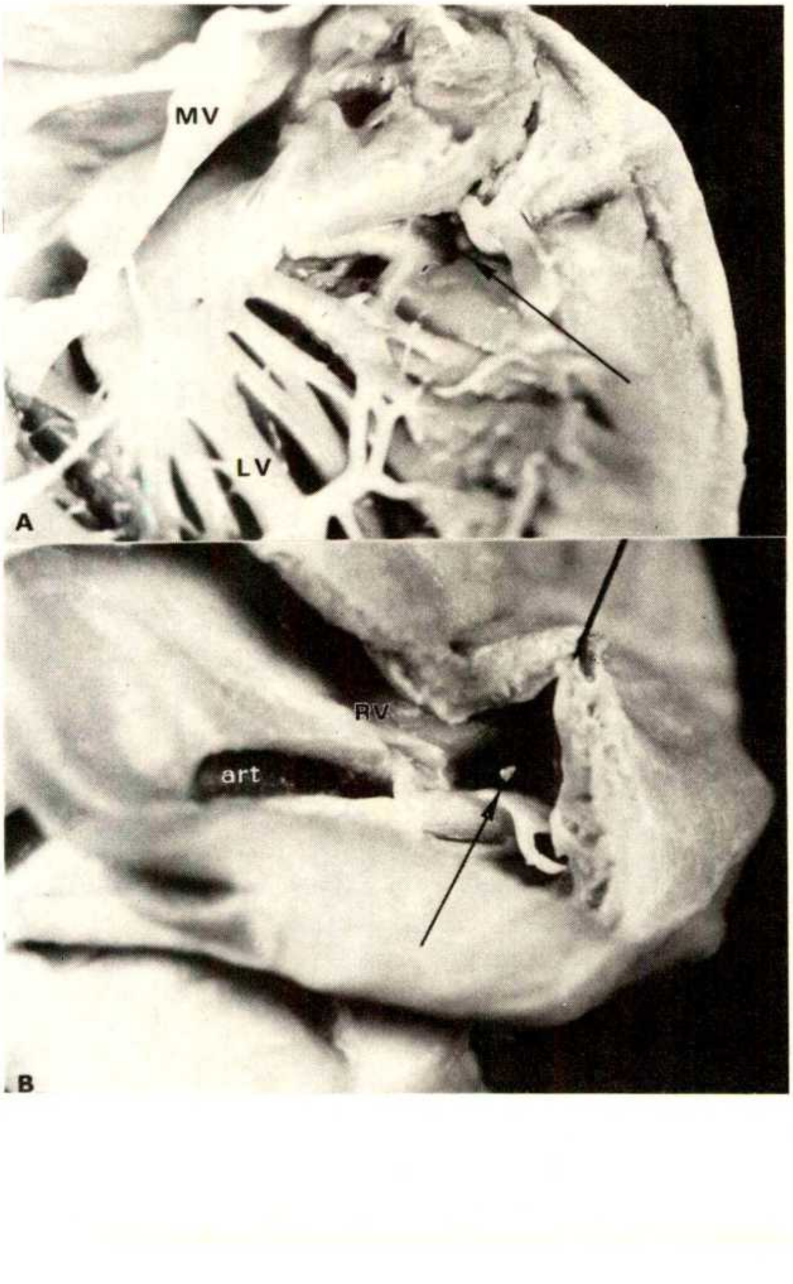


Fig. 2 *Photographs of the heart of Case 1. (A) Left ventricular aspect of ventricular septum showing an endothelialised recess (arrow) which ended blindly. With little force a probe could be passed from this recess into the right ventricle. (B) Right ventricular aspect of septum after removal of probe (light source on left ventricular side). Ventricular septal defect (arrow) is seen to enter right ventricle (RV). (See text for details.)*
Art, artefact; LV, left ventricle; MV, mitral valve.

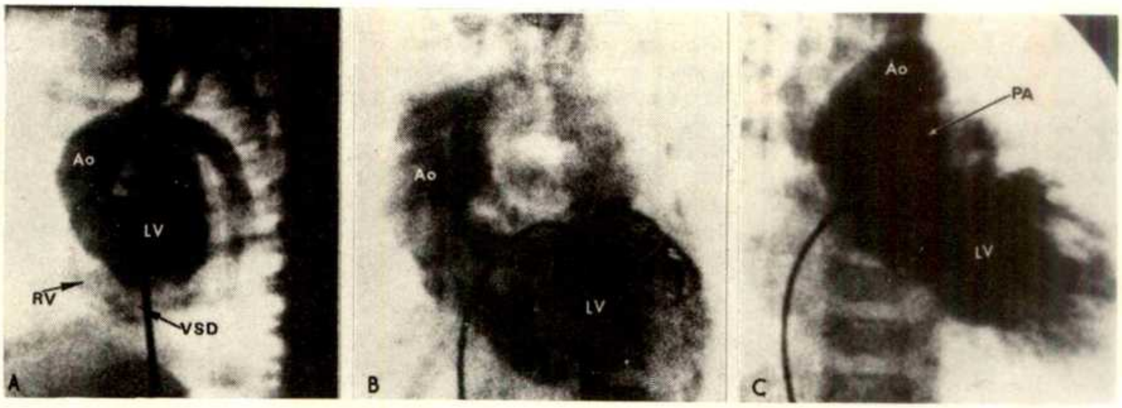


Fig. 3 *Case 3. (A) Left ventricular cineangiogram at 3 days of age. Left anterior oblique projection. Simultaneous opacification of aorta (Ao) and small crescent shaped right ventricle (RV) via small ventricular septal defect (VSD). Left ventricular cineangiograms at 1 year of age in left anterior oblique (B) and posteroanterior (C) projections show no ventricular septal defect. Note opacification of pulmonary artery (PA) from aorta via Waterston anastomosis in C.*

persistent ductus arteriosus. The calculated pulmonary-to-systemic flow ratio was greater than 2:1. After control of heart failure, the infant was discharged on treatment with oral digoxin and diuretics, but despite initial improvement, failed to gain weight. The physical findings two months later were unchanged except for prominent presystolic hepatic pulsation. A repeat catheterisation (Table 3) at that time showed a pressure gradient across the atrial septum suggesting obstruction at this site. This was relieved by balloon atrioseptostomy (Table 3) after which the presystolic hepatic pulsations disappeared; the infant improved and began to gain weight. She was examined regularly and at 12 months of age was considerably improved, with decrease in the heart size and pulmonary vascularity on *x*-ray suggesting a decrease in the size of the ventricular septal defect. The haemoglobin fell to about 15 g/dl at 4 months of age and rose to about 18 g/dl by 12 months of age concurrently with the decrease in pulmonary blood flow. The haemoglobin level remained unchanged over the next few months of life but began to rise steeply at 18 months of age. At 22 months because of high haemoglobin ($>$20 g/dl), considerably decreased exercise tolerance, and constant hyperpnoea, a Blalock-Taussig anastomosis was performed. Repeat chest *x*-ray taken at 21 months showed further diminution in cardiac size and pulmonary blood flow. After the shunt operation the symptoms improved and the haemoglobin fell to 16 g/dl. Fig. 4 relates changes in haemoglobin level to the clinical course.

CASE 5

This female infant was seen at the age of 5 months because of cyanosis, and on examination had a grade 4/6 pansystolic murmur at the left lower sternal border. The chest *x*-ray showed minimal cardiomegaly and decreased pulmonary vascularity.

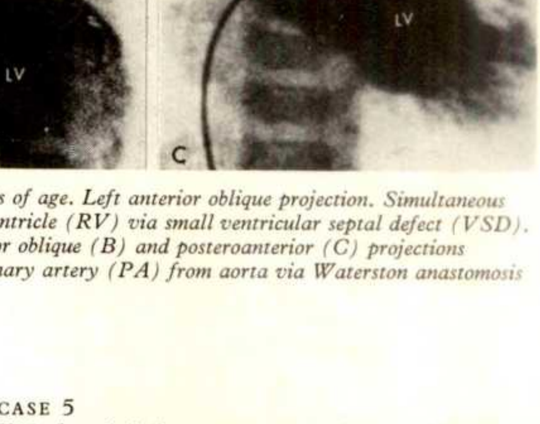


Fig. 4 *Case 4. Haemoglobin (g/dl) plotted against age in months. Note initial drop (by about 4 months) in haemoglobin to a near normal level, and gradual increase up to age of 18 months, followed by steep rise from 18 to 21 months of age (see text). The timings of the cardiac catheterisations and Blalock-Taussig (B-T) shunt are indicated. Note prompt fall in haemoglobin after shunt operation.*

The electrocardiogram showed a mean frontal plane vector of −75° and diminished anterior forces. The haemoglobin was 13·5 g/dl, and the haematocrit 42 per cent. A clinical diagnosis of tricuspid atresia was made. Because of increased cyanosis and easy fatiguability, a left Blalock-Taussig anastomosis was performed at the age of 13 months. She improved at first, but then symptoms recurred and the haematocrit increased significantly (Hb 20 g/dl and haematocrit 60%) at about the age of 3 years. Cardiac catheterisation and angiography confirmed the clinical diagnosis of tricuspid atresia with normally related great arteries. Left atrial angiogram in the left anterior oblique projection showed a moderate-sized ventricular septal defect (Fig. 5A). The Blalock-Taussig anastomosis was patent but small. She then had a Glenn operation, and again improved clinically, with fall in haemoglobin to

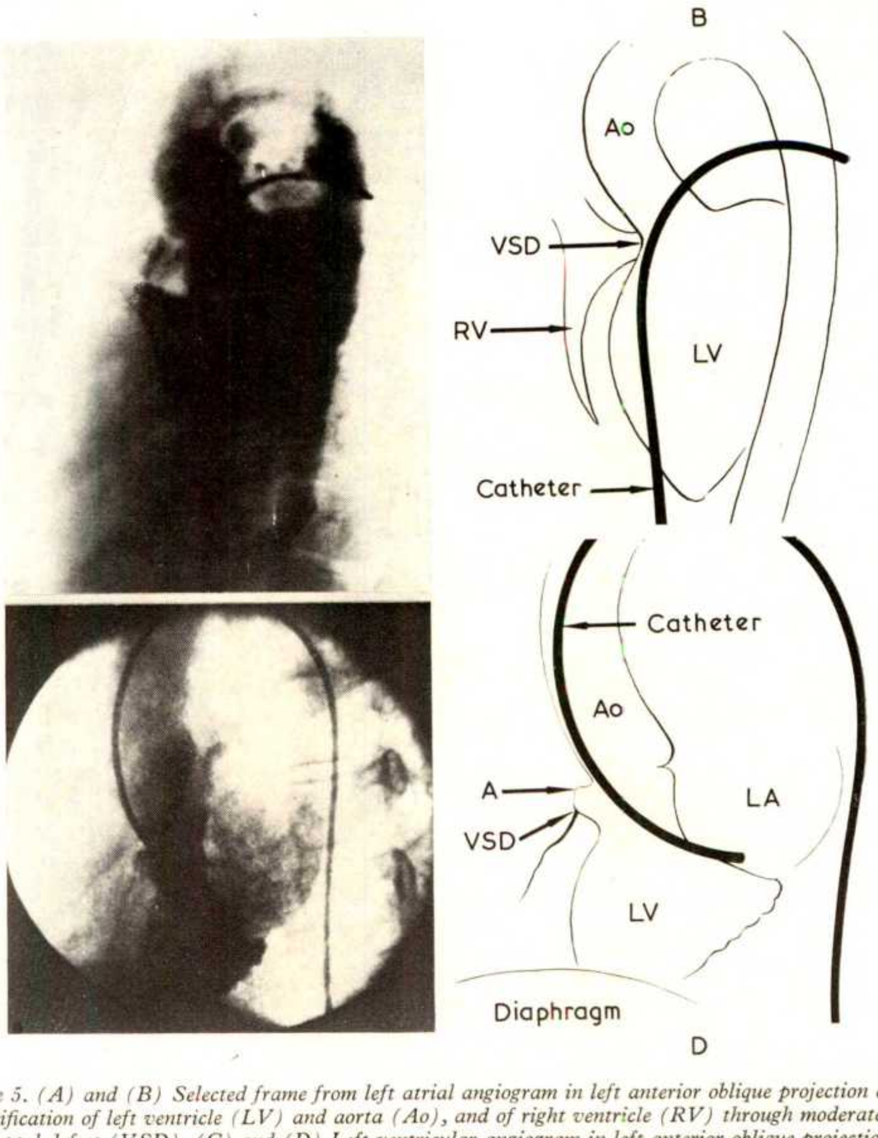


Fig. 5 *Case 5. (A) and (B) Selected frame from left atrial angiogram in left anterior oblique projection at 3 years showing opacification of left ventricle (LV) and aorta (Ao), and of right ventricle (RV) through moderate sized ventricular septal defect (VSD). (C) and (D) Left ventricular angiogram in left anterior oblique projection at 16 years shows aneurysm (A) of the ventricular septum with string-like jet through tiny ventricular septal defect (VSD). Minimal opacification of left atrium (related to catheter position).*

15 g/dl. During the ensuing years she developed increasing polycythaemia and worsening symptoms. At 16 years of age moderate cyanosis and clubbing, a short grade 1/6 systolic murmur at the left lower sternal border, and a grade 2/6 continuous murmur below the left clavicle. The electrocardiogram was unchanged. Chest *x*-ray showed minimal cardiomegaly and normal pulmonary vascularity. Haemoglobin was 20 g/dl. A repeat cardiac catheterisation (Table 3) at this time confirmed the diagnosis of tricuspid atresia with normally related great vessels. The Glenn anastomosis was functioning well and Blalock-Taussig anastomosis showed obvious narrowing at the junction of the left subclavian and left pulmonary arteries. A selective left ventriculogram in the left anterior oblique projection showed an aneurysm of the membranous ventricular septum and a ventricular septal defect of pin-hole size at the apex of the aneurysm (Fig. 5B). At the time of Fontan operation the ventricular septal defect was 2 mm in size. She improved considerably after this operation.

CASE 6

This 14-year-old girl presented with severe congestive heart failure at 4 months of age. A pulmonary artery banding operation was performed and she improved clinically. At cardiac catheterisation and angiography performed elsewhere when she was 9 months old, a diagnosis of tricuspid atresia with transposition of the great arteries was made. She remained well on treatment with digitalis. When first seen by our group at 4 years, the physical findings were cyanosis and clubbing, a thrill in the suprasternal notch, a grade 3/6 pansystolic murmur at the lower left sternal border, and a grade 4/6 ejection systolic murmur at the upper left sternal border, and a single second heart sound. Chest *x*-ray showed cardiomegaly and increased pulmonary vascularity. The electrocardiogram showed a mean frontal plane vector of +60°, and left atrial and left ventricular hypertrophy. The haematocrit was 45 per cent. Cardiac catheterisation with selective cineangiography at 5 years (Table 3) confirmed the diagnosis of tricuspid atresia with transposition of the great arteries, moderate to large ventricular septal defect with a small right ventricle (Fig. 6A), and supravalvar pulmonary artery stenosis (pulmonary artery banding). She continued well with only minimal exercise intolerance, until at 13 years of age, she developed a brain abscess which resolved with treatment. At the age of 14 years, she had moderate cyanosis and clubbing, diminished femoral pulses, a grade 3/6 ejection systolic murmur with thrill at the upper right sternal border with radiation into the carotids, and a single second heart sound. Catheterisation (Table 3) and angiography confirmed the previous diagnoses; additional findings included coarctation of the aorta, normal pulmonary artery pressure beyond the surgically

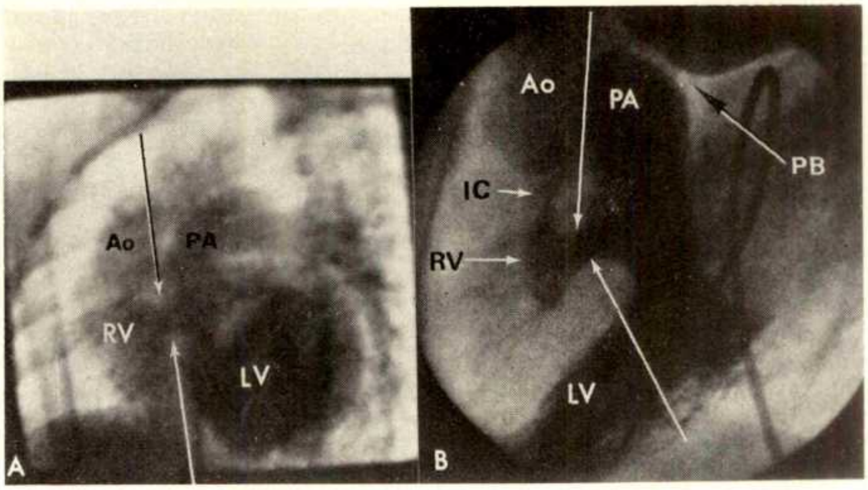


Fig. 6 *Case 6. Left ventricular angiograms in left anterior oblique projection performed at 5 years (A) and 14 years (B). Posterior pulmonary artery (PA) is opacified from left ventricle (LV). Pulmonary artery band (PB) is clearly seen in (B). Right ventricle (RV) and anterior aorta (Ao) opacify from left ventricle via ventricular septal defect (marked by the arrows). Ventricular septal defect appears to be relatively smaller in (B) than in (A); defect is smaller than aortic valve in (B). Infundibular constriction (IC) is distinctly seen in (B).*

created pulmonary band, and what appeared to be a small ventricular septal defect and narrow right ventricular outflow tract (Fig. 6B). The patient had the coarctation resected, and is now awaiting a modified Fontan operation, with bypass of ventricular septal defect and right ventricle by anastomosis of the proximal stump of the divided main pulmonary trunk to the ascending aorta (Stansel, 1975).

Discussion

Of the 6 cases described, 3 had complete and spontaneous anatomical closure of ventricular septal defects, and the findings in the other 3 cases are consistent with partial closure. For the purpose of analysis, two previously reported cases (Rao and Sissman, 1971; Rao *et al.*, 1974) can be added to this group, which then consists of 4 cases with complete closure and 4 with partial closure. Two of the patients with complete closure (Case 1 of Rao and Sissman (1971) and Case 1 of this report) became severely hypoxic and died. In the other 2 patients (Cases 2 and 3 of this report), the decrease in pulmonary blood flow caused by closure of the ventricular septal defect may not have significant clinical effect because of the earlier systemic-pulmonary shunts (Glenn anastomosis in one and Waterston shunt in the other). In 2 of the cases with partial closure of ventricular septal defect (Case 3 of Rao *et al.* (1974) and Case 4 of this report), the congestive heart failure improved, but in Case 4, progressive closure of the defect resulted in severe hypoxia, so that a Blalock-Taussig operation had to be performed. In the fifth case of this report, closure of the ventricular septal defect might have contributed to the decreased pulmonary blood flow but this effect was obscured by the surgical shunts. The sixth case is the only case of tricuspid atresia with transposition of the great arteries in which there seems to be some evidence for closure of the ventricular septal defect. Despite what appeared to be a small ventricular septal defect by angiography (Fig. 6B), no systolic pressure gradient was detected on withdrawal from the left ventricle to the right ventricle across the defect. Ross and Somerville (1973) reported one case of tricuspid atresia with transposition in which no pressure gradient was detected between the ventricles, but in which at necropsy the ventricular septal defect was small. The absence of pressure gradient in both these cases may be attributed to the phenomenon of 'stenosis without pressure gradient' in the presence of multiple obstructions in series (Silove *et al.*, 1968; Rao and Linde, 1974); it has been observed that there may be no pressure gradient across a proximal obstruction in the cardiovascular system (Silove *et al.*, 1968; Rao and Linde, 1974).

Increasing cyanosis with a rise in the haematocrit was present in most cases; this was more pronounced when there was complete closure of the ventricular septal defect than when this was partial. Disappearance of a previously heard pansystolic murmur was seen in all 4 cases with complete closure and decreased heart size and/or decrease in pulmonary vascularity occurred in 6 of the 8 cases.

Complete closure of the ventricular septal defect in tricuspid atresia has previously been reported in only a few cases (Roberts *et al.*, 1963; Meng 1969; Rao and Sissman 1971; Bargeron *et al.*, 1972). The clinical features of the reported cases were similar to ours. Partial closure of ventricular septal defect in tricuspid atresia has also been reported previously (Gallaher and Fyler, 1967; Marcano *et al.*, 1969; Dolara *et al.*, 1969; Rao *et al.*, 1974). Gallaher and Fyler (1967) reported 3 patients with tricuspid atresia who had cardiac failure and pulmonary plethora during infancy; over varying periods of time they became more cyanotic; cardiomegaly and pulmonary blood flow decreased; finally they required palliative shunt procedures to relieve symptoms of hypoxia. They suggested reduction in size of the ventricular septal defect as a possible cause of decreasing pulmonary blood flow in tricuspid atresia. Marcano *et al.* (1969) and Dolara *et al.* (1969) reported similar cases and postulated a closing ventricular septal defect as the most likely cause of diminution of pulmonary blood flow in tricuspid atresia. These observations suggested that the obstruction to pulmonary blood flow in tricuspid atresia is at the level of the ventricular septal defect but no physiological proof for this could be provided. Rao *et al.* (1974) reported a case (their Case 3) in support of this suggestion: a pressure record during withdrawal from the pulmonary artery to the right ventricle and then to the left ventricle showed a pressure gradient between the ventricles (MPA 28/10 → RV 28/4 → LV 80/6). This and the reports of complete and spontaneous anatomical closure of a ventricular septal defect in tricuspid atresia support the view that the obstruction is at the level of the ventricular septum.

Apart from the *anatomical* closure of ventricular septal defect in tricuspid atresia, intermittent and *functional* closure of these defects can also occur (Rao and Linde 1973; Rao *et al.*, 1974), causing cyanotic spells in tricuspid atresia.

The incidence of closure of the ventricular septal defect in tricuspid atresia is difficult to estimate accurately because of the small number of cases reported. The 6 cases reported here were from a series of 20 cases, giving an incidence of 30 per cent.

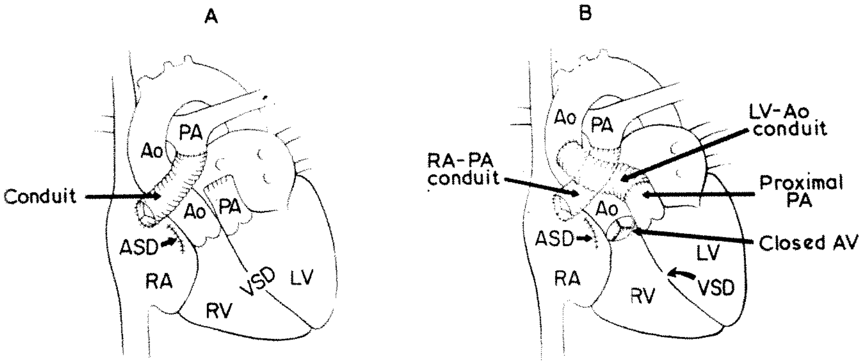
However, since type IA cases do not have ventricular septal defects these cases may be excluded; thus, 38 per cent (6 of 16) can be taken as the true incidence of spontaneous closure of ventricular septal defect in tricuspid atresia; this is similar to the incidence of spontaneous closure of isolated ventricular septal defect (Bloomfield, 1964; Hoffman and Rudolph, 1965; Hoffman and Rudolph, 1970; Keith *et al.*, 1971). The age at which the ventricular septal defect closes appears to vary; in 4 closure was noted before 2 years of age (1 before 6 months and 1 before 12 months), in 3 after the age of 2 years, and in 1 between the ages of 2 and 60 months.

Several different mechanisms of closure of ventricular septal defects have been postulated. The necropsy specimens examined by the author during this and other studies (Rao and Sissman, 1971; Rao *et al.*, 1973, 1974) and by Guller and Titus (1968) have shown that the ventricular septal defect, in most cases of tricuspid atresia is located in the muscular septum and that the defect is surrounded entirely by muscle. Therefore, progressive muscular 'encroachment' at the margins of the defect with subsequent fibrosis and covering by endocardial proliferation (Roberts *et al.*, 1963; Meng, 1969; Rao and Sissman, 1971) seems the most probable mechanism of closure in tricuspid atresia; this view is supported by the necropsy findings in Case 1. However, in Case 5 the ventricular septal defect appears to have closed by formation of an aneurysm of the ventricular septum as previously described (Varghese *et al.*, 1969; Freedom *et al.*, 1974) in isolated ventricular septal defects.

The factors initiating the closure of ventricular septal defect, if any, are not known. Because closure of the ventricular septal defect occurred in cases with or without previous systemic-pulmonary shunt operations, it is reasonable to assume that the closure of the defect in tricuspid atresia is not initiated or accelerated by surgical shunts. It appears that there is a great natural tendency for a ventricular septal defect to close spontaneously, whether it is an isolated defect or part of a more complex cardiac anomaly like tricuspid atresia, double outlet right ventricle (Edwards *et al.*, 1952; Rao and Sissman, 1971; Rao, 1974), or transposition of the great arteries (Rao, 1972, 1974); the reason for this remains unclear.

Hitherto, only palliative surgical treatment was available, but recently Fontan and his associates (Fontan *et al.*, 1971; Fontan and Baudet, 1971) have devised an operation for physiological correction of tricuspid atresia. Published reports (Fontan and Baudet, 1971; Ross and Somerville, 1973; Stanford *et al.*, 1973; Kreutzer *et al.*, 1973; Miller *et al.*, 1974; Henry *et al.*, 1974; Walker *et al.*, 1975; Kreutzer, 1975) suggest that successful surgical correction of tricuspid atresia can be performed in patients older than 8 years. Patients with tricuspid atresia most commonly present with symptoms in infancy and these babies should be effectively palliated to enable them to reach the age at which surgical correction can be undertaken. The palliative procedures used are the Glenn operation and various types of systemic artery-to-pulmonary artery anastomosis. Because of the high incidence of spontaneous closure of ventricular septal defects in tricuspid atresia, the Glenn anastomosis may not be an appropriate palliative procedure. Should the ventricular septal defect close after a Glenn shunt, the left pulmonary circuit will be without blood flow. Additional reasons for avoiding a Glenn anastomosis in the symptomatic patient with tricuspid atresia are the long-term complications seen with this type of shunt procedure (Glenn, 1969; Achtel *et al.*, 1969; Boruchow *et al.*, 1969, 1970; Sakiyalak *et al.*, 1971; Bargeron *et al.*, 1972; Willman *et al.*, 1974). Thus, a systemic artery-to-pulmonary artery shunt is preferable. Whether a Blalock-Taussig (subclavian artery-pulmonary artery) or Waterston or Potts (aortopulmonary) shunt should be performed in a given case usually depends upon the size of the pulmonary vessels. But, because central aortopulmonary shunts may result in raised pulmonary arterial pressure and resistance, and because the right atrium may not be able to maintain adequate pulmonary blood flow against this resistance after a Fontan operation (Fontan and Baudet, 1971; Kreutzer *et al.*, 1973), central aortopulmonary shunts should be avoided. Thus, a Blalock-Taussig anastomosis is the palliative procedure of choice for tricuspid atresia. Should additional palliation be required before the patient attains the age and size suitable for a Fontan operation, a Blalock-Taussig operation on the opposite side can be performed.

The Fontan operation can also be employed for correction of tricuspid atresia with transposition (Fontan and Baudet, 1971; Ross and Somerville, 1973). This involves disconnecting the pulmonary artery from the left ventricle and anastomosing it to the right atrium via a valved conduit as well as the other steps of the Fontan operation (Fig. 7A). After this operation, the left ventricle has to pump blood into the aorta via the ventricular septal defect and the right ventricle. An adequate size of ventricular septal defect and right ventricle without obstruction is essential for a successful operation. Though the patient with type II tricuspid atresia operated on by Fontan and Baudet (1971) survived, a patient treated similarly by Ross and Somerville (1973) died



Fontan for tricuspid atresia with transposition

Fontan for tricuspid atresia with transposition and small VSD

Fig. 7 (A) Fontan operation for tricuspid atresia with transposition of the great arteries involves insertion of valved conduit between right atrium (RA) and pulmonary artery (PA) and closure of atrial septal defect (ASD). Blood from left ventricle (LV) must then flow to aorta (Ao) via ventricular septal defect (VSD) and right ventricle (RV). (B) A small ventricular septal defect results in subaortic obstruction which is bypassed by connection of proximal stump of divided PA to ascending aorta either directly or via LV-Ao conduit; the aortic valve (AV) is closed. The principles of this suggested operation are adopted from Stansel (1975).

of low cardiac output in the immediate postoperative period. This was attributed to subaortic obstruction caused by the small ventricular septal defect. In our case (Case 6), despite the absence of a pressure gradient across it, the ventricular septal defect appeared small angiographically. Therefore, the size of the defect should be assessed preoperatively, both by pressure measurements across it and by angiography. The size of the ventricular septal defect should also be assessed at the time of operation by inspection and/or palpation through the aortic root (Ross and Somerville, 1973). If the ventricular septal defect is found to be small it may be necessary to resect ventricular septal muscle to enlarge it, as suggested by Ross and Somerville (1973). Alternatively, the ventricular septal defect, right ventricle, and aortic valve may be bypassed by anastomosis of the proximal stump of the divided main pulmonary artery to the ascending aorta at the time of the Fontan operation (Fig. 7B), as suggested by Stansel (1975) for correction of transposition of the great arteries. If the pulmonary arterial stump is too short, a prosthetic conduit can be inserted between it and the ascending aorta.

Clinical deterioration and decreasing intensity of a previously heard systolic murmur in patients with complex congenital heart disease should lead one to suspect closure of the physiologically advantageous ventricular septal defect. A complete understanding of the circumstances surrounding the spontaneous closure of these defects and appreciation of the true nature of the changing anatomical and haemodynamic state should result in more rational and effective therapy.

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Coronary artery occlusion and alcohol intake

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A group of over 900 patients who underwent coronary arteriography were asked about their alcohol intake. The patients who were abstainers or consumed less than an equivalent of 180 ml absolute alcohol per week had higher coronary artery occlusion scores than the group consuming more than that amount, though the latter group smoked more and had higher plasma triglyceride levels.

Studies dealing with a possible association between alcohol intake and the development of coronary artery disease, or relating alcohol intake to changes in some variables associated with coronary artery disease, have produced conflicting results. Most reports have shown that moderate to excessive alcohol consumption leads to increased blood lipid levels (especially triglyceride levels), in chronic alcoholics (Albrink and Klatskin, 1957; Zieve, 1958; Lieber *et al.*, 1963), in patients with type IV hyperlipoproteinaemia (Mendelson and Mello, 1973; Ginsberg *et al.*, 1974), and even in presumably normal individuals (Ostrander *et al.*, 1974; Wilson *et al.*, 1970; Barboriak and Meade, 1968). Since high plasma lipid levels are usually associated with a higher incidence of cardiovascular disease (Albrink *et al.*, 1961; Kannel *et al.*, 1971; Carlson and Bottinger, 1972), one might have expected a similar tendency to higher incidence of heart disease in regular imbibers of alcoholic beverages. However, studies relating alcohol intake directly to development of coronary artery disease have failed to show a consistent relation. Most necropsy data suggest either no clear relation to coronary artery disease (Sackett *et al.*, 1968) or less extensive atherosclerotic lesions in coronary arteries of patients with chronic alcoholism than in abstainers (Rissanen, 1974; Wilens, 1947a).

The apparent discrepancy between the effect of alcohol on plasma lipids and the absence of correlation between alcohol consumption and atherosclerosis may be partially the result of differences in study populations. While the blood lipid studies were usually carried out in populations consisting mainly of abstainers and moderate drinkers, most of the necropsies were on patients with advanced alcoholism, many of whom had suffered from other debilitating diseases usually associated with excessive chronic alcohol intake (Wilens, 1947b). The availability of data from a follow-up study of patients who had had coronary arteriograms, who were also repeatedly questioned as to their alcohol intake, gave us the opportunity to study in the same group of patients, both the association between alcohol intake and plasma lipid levels, and the association between alcohol intake and coronary arterial obstruction as shown by angiography.

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Methods

A group of 909 male nondiabetic patients had selective coronary angiograms in two Milwaukee hospitals over a 4-year-period. The indications for coronary angiography were angina pectoris, previous myocardial infarction, chest pain on stress test, or chest pain associated with strong family history of heart disease. Each patient answered a self-administered life quality questionnaire which contained questions on the current alcohol intake, including the frequency, amount, and type of alcoholic beverage consumed. The alcohol intake, in ml per week of absolute alcohol, was then calculated using the usual alcohol concentration values (4% for beer, 12% for wine, and 43% for 'hard' liquor). In order to find out whether the information on alcohol intake reflected a regular drinking habit, 413 patients were asked to answer the questionnaire again one year later. An equivalent of 60 ml absolute alcohol per week was taken as a dividing line between regular and occasional drinking. Over 80% of the group continued to consume more than this amount, indicating a relative stability of the habit.

The extent of coronary artery disease was recorded as a 'coronary artery occlusion score', the method of calculation being based on that of Rowe *et al.* (1969). Each of the three major coronary arteries (right, left anterior descending, and left circumflex) is given a score from 0 (normal) to 100 (complete occlusion). Thus, 50 per cent occlusion of the left anterior descending artery would score 50; 50 per cent occlusion of a branch estimated to be 50 per cent of the size of the parent vessel would score 25; the left main coronary artery is scored from 0 to 200, so that 50 per cent occlusion of this vessel would score 100.

Plasma cholesterol and triglyceride levels were determined on fasting blood samples obtained shortly before the cardiac catheterisation.[1]

Information about hypertension, smoking habits, and previous myocardial infarction was obtained by direct questioning of the patients and from their medical records. Smoking habit, past and present, was graded on a 5-point scale:

(1) Not currently smoking and no history of smoking.
(2) Less than ½ package per day for less than 20 years.
(3) One package per day for less than 20 years or ½ package per day for more than 20 years.
(4) One and one-half packages per day for 10 to 30 years, 2 packages per day for less than 20 years, or 1 package per day for more than 20 years.
(5) Two packages or more per day for 20 years or 1½ packages or more per day for 30 years.

Results

To correct for the known association between age and coronary artery disease, the patients were divided into four different age groups (Table 1). The average coronary artery occlusion score for combined groups (all ages) of the abstainers and moderate drinkers was 145, and this was significantly higher (P < 0·01) than the combined scores of 123 for the patients with high and very high alcohol intake. This negative association between occlusive disease and alcohol consumption was evident for all but the youngest age groups. It is interesting to note that a weekly alcohol intake of 180 ml seemed to be a dividing point in alcohol consumption associated with high and low coronary artery occlusion scores. The patients who were abstainers or ingested less than 180 ml per week had similar relatively high scores. The coronary artery occlusion scores of the two groups of patients who drank more than 180 ml per week were also similar but lower than in the two other groups. As expected, there was a significant increase in the coronary artery occlusion score with ageing of the patients.

To determine whether this negative correlation between drinking and coronary artery occlusion score could be attributed to some change in other risk factors which may be associated with drinking, plasma cholesterol and triglyceride levels, history of smoking, the presence of hypertension, and history of previous myocardial infarction were also considered. Data in Table 2 show that there was a statistically significant difference between the individual alcohol intake groups and average smoking scale, higher alcohol intake being associated with higher smoking scale. There was also a statistically significant difference in plasma triglyceride between the four alcohol intake groups, higher alcohol intake being associated with higher triglyceride level. Prevalence of hypertension,

Table 1 *Coronary artery occlusion score and alcohol consumption of patients with angiographic examination*

	Alcohol intake per week (ml) *0*	*<180*	*180–360*	*>360*	*All intakes of alcohol combined*
Age <40	41 (14)*	73 (34)	83 (22)	82 (19)	72 (89)
Age 40–49	147 (41)	125 (120)	108 (52)	120 (43)	125 (256)
Age 50–59	154 (59)	160 (196)	132 (85)	134 (64)	149 (404)
Age >60	170 (36)	173 (67)	152 (39)	120 (18)	161 (160)
All ages combined	145 ±90 (150)	145 ±88 (417)	125 ±88 (198)	121 ±86 (144)	137 ±89 (909)
	145	P < 0 01	123		

*Number of patients in parentheses
Overall correlation between coronary artery occlusion score and age: P < 0 01.
Overall correlation between coronary artery occlusion score and alcohol intake: P < 0 01.

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[1] The procedure used for these determinations in our laboratory (Kessler and Lederer, 1965; Block *et al.*, 1965) passed the certification requirements of the Cooperative Cholesterol and Triglyceride Standardization Program, Center for Communicable Diseases, Atlanta, Georgia.

Table 2 *Plasma cholesterol and triglyceride levels, extent of smoking experience, and prevalence of hypertension and previous myocardial infarction in patients with angiographic examination*

		Alcohol intake per week (ml)				*All intakes of alcohol combined*
		0	*< 180*	*180–360*	*> 360*	
		Age <40				
Plasma cholesterol (mg/100 ml)	(C)	219	229	251	229	233
Plasma triglycerides (mg/100 ml)	(T)	172	150	178	205	172
Smoking scale	(S)	2·5	2·8	3·1	3·6	3·0
Hypertension (%)	(H)	36	26	41	37	34
Previous myocardial infarctions (%)	(MI)	29	50	41	42	43
		Age 40–49				
	(C)	258	250	246	267	253
	(T)	178	178	217	207	191
	(S)	3·8	3·4	3·9	3·8	3·6
	(H)	32	26	23	35	28
	(MI)	63	56	63	44	57
		Age 50–59				
	(C)	242	246	252	249	247
	(T)	160	184	181	212	184
	(S)	3·5	3·3	3·6	3·8	3·5
	(H)	34	41	28	48	39
	(MI)	51	64	46	55	57
		Age > 60				
	(C)	253	234	238	245	240
	(T)	160	174	150	182	166
	(S)	3·1	3·2	3·8	4·2	3·4
	(H)	44	19	32	39	30
	(MI)	42	51	39	39	45
		All ages combined				
	(C)	247	244	248	251	246 ±51*
	(T)	166	178	184	206†	182 ±93
	(S)	3·4	3·3	3·6	3·8†	3·5 ±1·3
	(H)	36	32	29	42	34
	(MI)	50	58	49	47	53

*Standard deviation.

†Significant correlation with alcohol consumption: P < 0·01 (calculated for all ages combined only).

Conversion factor from Traditional Units to SI Units: cholesterol, 1 mg/100 ml≈0·0259 mmol/l; triglycerides, 1 mg/100 ml≈0·0113 mmol/l.

previous myocardial infarction, and plasma cholesterol did not show any consistent correlation with alcohol intake.

Discussion

The results of the present study indicate that patients with angina pectoris and/or a previous myocardial infarction, who also consumed large amounts of alcohol, showed less arteriographically demonstrable occlusive coronary artery disease than the abstainers or moderate drinkers. This reduced extent of coronary artery disease was especially remarkable in patients consuming more than 360 ml alcohol weekly, since they also had increased plasma triglyceride levels and a high proportion of heavy smokers, and were thus a group which could be considered to be at a higher risk of developing coronary artery disease (Albrink *et al.*, 1961; Sackett and Winkelstein, 1967).

Other investigators observed a similar reduced tendency to develop certain features of coronary heart disease in imbibers of alcoholic beverages. Klatsky *et al.* (1974), investigating the prevalence of myocardial infarction in a group of 464 patients, found this to be higher in teetotallers than in regular drinkers. Rissanen (1974) compared the extent of coronary artery lesions found at necropsy in age-matched chronic alcoholics and presumably non-alcoholic victims of accidents. He found significantly smaller areas of fatty streaks in the former group; however, the severity of raised lesions was about equal. Goto *et al.* (1974) found a delay and reduction in the development of atherosclerosis in rabbits receiving alcohol along with their atherogenic diet. The findings in this study and other published data thus indicate the possibility that ingestion of alcohol may have some retarding effect on the development and progression of occlusive coronary artery disease.

In other studies, however, there was little or no association between alcohol intake and the development of heart disease. Sackett *et al.* (1968) attempted to correlate the consumption of alcohol with the extent of coronary artery lesions determined at necropsy in 1010 cancer patients but found no significant association. Alcohol intake in their patients was, however, much lower than in this and other studies (Klatsky *et al.*, 1974). It is possible that some patients with malignant disease consume less alcohol (Bichel, 1959) or that the presence of malignant disease may have affected the course of coronary artery disease.

Hirst *et al.* (1965) found fewer coronary artery lesions in patients with hepatic cirrhosis than in chronic alcoholics who did not have cirrhosis. Unfortunately, no definite information is available on the possible presence of cirrhosis in our patients. Since most of the patients continued in gainful employment, it is likely that the prevalence of serious hepatic cirrhosis was relatively low. In a study of excessive alcohol consumption in ischaemic heart disease, in twins with differing alcohol intake, Myrhed (1974) failed to find any significant differences in the major indicators of ischaemic heart disease; however, the studied populations were quite young and there were no cases of myocardial infarction in either group.

The increase in plasma triglyceride levels in parallel with alcohol intake confirms the previously reported findings of Ostrander *et al.* (1974), showing a lipaemic effect of regular alcohol intake even in a non-alcoholic population. Our results further suggest that, under certain circumstances, a substantial increase in fasting plasma triglyceride may not be associated with increased coronary artery obstruction. It is possible that an increase in both plasma cholesterol and triglyceride is needed to accelerate progression of coronary atherosclerosis. In our previous study (Barboriak *et al.*, 1974), the extent of angiographically demonstrable coronary artery disease correlated better with increased plasma cholesterol than plasma triglyceride levels. The absence of any consistent relation between increasing amounts of ingested alcohol and plasma cholesterol levels in this study may thus be one of the reasons for the observed lower coronary artery occlusion scores of patients with high alcohol intake. However, it is also possible that these lower coronary artery occlusion scores are the result of the known cardiotoxic effects of alcohol, not directly related to the extent of coronary artery disease. It has been shown that alcohol depresses myocardial function in patients with heart disease (Conway, 1968), reduces myocardial contractility (Ahmed *et al.*, 1973), leads to other myocardial abnormalities (Wong, 1974; Alexander, 1975), and aggravates exercise-induced angina (Orlando *et al.*, 1976). It is possible that a chronic intake of excessive amounts of alcohol has produced more severe symptoms than would be expected on the basis of the extent of the coronary artery disease.

It should also be stressed that the present study was carried out in patients with symptoms of coronary artery disease. It remains unclear whether, and to what extent, this group may differ from the general population with respect to alcohol intake, susceptibility to the effects of alcohol, possible genetic factors, and other variables affecting development of coronary artery disease.

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Rheumatic aortic stenosis in young patients presenting with combined aortic and mitral stenosis

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This report describes 30 patients under the age of 30 years with rheumatic aortic stenosis, presenting with combined aortic and mitral stenosis. Three patients had additional tricuspid stenosis. Twenty-eight patients gave a history of rheumatic polyarthritis. The diagnosis was confirmed by right and left heart catheterisation in all. The murmur of aortic stenosis was not initially present in 8 out of 10 patients in congestive heart failure. Aortic valve calcification was not seen. Cineangiography showed a tricuspid aortic valve in all, unlike congenital aortic stenosis. A unique feature of this group was the raised pulmonary vascular resistance in 87 per cent of the patients. The present study shows that patients in India developing aortic stenosis after rheumatic fever do so early in the natural history of the disease.

Rheumatic heart disease is well known to be the main cardiac disease in India (Hughes and Yusuf, 1930; Mathur, 1960; Padmavathy and Datey, 1970). There are differences between rheumatic heart disease as seen in India and as reported from Western countries. In India, isolated severe rheumatic mitral stenosis occurs in a much younger age-group and about 30 per cent of mitral valvotomies are done in patients below the age of 20 (Roy *et al.*, 1963; Cherian *et al.*, 1964; Shah, 1974). Much has been written about juvenile mitral stenosis in India (Vytilingam *et al.*, 1970) and in countries like Sri Lanka (Paul, 1967), Thailand (Jumbala *et al.*, 1970), Turkey (Ozcan *et al.*, 1970), and Israel (Borman *et al.*, 1961), but there have been no reports describing the occurrence of rheumatic stenosis of the aortic valve in the younger age-group. This may partly be the result of the difficulty in differentiating rheumatic aortic stenosis from congenital aortic stenosis without aortography. On reviewing the published reports on combined aortic and mitral stenosis (Table 1) we find that most of the patients were above the age of 30 years. The present report is based on a study of 30 patients below 30 years with combined aortic and mitral stenosis.

Table 1 *Rheumatic aortic stenosis in young patients*

	No. of cases reported	*No. of cases below 30 years*	%
Katznelson *et al.* (1960)	22	Nil	0
Honey (1961)	35	2	5·7
Reid *et al.* (1962)	15	1	6·6
Zitnik *et al.* (1965)	10	Nil	0
Schattenberg *et al.* (1967)	35	3	8·5
Present series (1976)	50	30	60

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Subjects and methods

During the past 5 years (1970–1975) we have had 50 patients with combined aortic stenosis and mitral stenosis, of whom 30 were below the age of 30 years. Patients were drawn from all over India.

After a detailed clinical history had been obtained a complete physical examination was made. All patients had a posteroanterior chest *x*-ray film and a right anterior oblique film with barium in the oesophagus; fluoroscopy with an image intensifier was used to detect mitral and aortic valvar calcification. Later, all patients had right and left heart catheterisation studies under light sedation using phenobarbitone and promethazine hydrochloride. Pressures were recorded using a Statham P23 Db pressure transducer connected to an Electronics for Medicine 8 Channel photographic recorder. Simultaneous pulmonary artery wedge and left ventricular pressure records were obtained in 20 patients. The remaining 10 patients had transeptal left atrial

Table 2 *Interval between first attack of rheumatic fever and onset of symptoms*

No. of years	*No. of patients*	%
< 2	Nil	0
2–5	3	10·7
6–10	6	21·4
11–20	17	60·7
> 20	2	7·2

catheterisation, with simultaneous recording of left atrial and left ventricular pressures. The aortic valve gradient was measured in 15 patients on a withdrawal record from left ventricle to aorta; simultaneous left ventricular and aortic pressure recordings were used in the remaining 15 patients, the left ventricle being entered in 10 by transeptal catheterisation, and in 5 by direct left ventricular puncture. Cardiac output was calculated using the Fick principle.

Results and analysis

AGE AND SEX INCIDENCE

Ages varied from 15 to 30 years. Twelve patients were between 10 and 20 years, and 18 were between 21 and 30 years. There were 23 male and 7 female patients.

HISTORY OF RHEUMATIC FEVER

Twenty-eight patients (93%) gave a history of migratory polyarthritis in childhood, suggestive of rheumatic fever. One patient had only a single attack, while all the others had recurrent attacks. None gave a history of chorea or rheumatic skin manifestations. The interval between the first attack of rheumatic fever and onset of dyspnoea on effort is shown in Table 2. The shortest interval was 5 years.

PRESENTING SYMPTOMS

These are shown in Table 3. All patients complained of exertional dyspnoea. This was grade 1 in 1 patient, grade 2 in 14, grade 3 in 11, and grade 4 in 4 patients. Four patients gave a history of recurrent paroxysmal nocturnal dyspnoea. Angina on effort was present in 11 patients. Ten patients were in congestive heart failure.

Table 3 *Presenting symptoms*

	No. of patients	%
Dyspnoea	30	100
Palpitation on exertion	15	50
Angina on effort	11	36
Haemoptysis	4	13
Syncope	2	6
Dependent oedema	10	33

PHYSICAL SIGNS

The arterial pulse was not anacrotic in any of our patients, but the pulse volume was small in 26 and increased by associated aortic regurgitation in 4. Cardiomegaly was present in 28 patients, and was massive in 3. A powerful apical impulse was seen and felt in 13 patients, while in another 15 the impulse was tapping in nature with a palpable shock of a loud first sound and a diastolic thrill. A systolic thrill was felt in the aortic area in 16 patients; in most instances, this thrill was faint and felt only in expiration with the patient leaning forward. A left parasternal heave was present in 27 patients. All the patients had an accentuated pulmonary closure sound, and 17 had palpable pulmonary artery pulsations and a palpable pulmonary closure sound. Aortic closure was soft in 15 patients. A clear mitral opening snap was audible in 24 patients and an aortic ejection click in 10; both an ejection click and an opening snap were present only in 4 patients. A full length mitral diastolic murmur was present in all except 3, one of whom had only a mid-diastolic murmur, the other 2 having no mitral diastolic murmur at all. Twelve patients had apical systolic murmurs. An ejection systolic murmur in the aortic area was audible in 28 patients; in 8 out of the 10 patients with congestive cardiac failure, the murmur was heard only after this had been controlled. In the other 2 patients aortic stenosis was diagnosed only at cardiac catheterisation. A soft blowing early diastolic murmur at the left sternal border was a common finding, and was heard in 22 of our patients; this was proved to be due to aortic regurgitation by angiography. Ten patients were in congestive heart failure. In 3 of these, it was not possible to control the cardiac failure adequately; the jugular venous pressure remained high with prominent *a* waves, and the presence of associated tricuspid stenosis was confirmed at cardiac catheterisation.

ELECTROCARDIOGRAM

The electrocardiographic features are shown in Table 4. Left ventricular hypertrophy alone or combined with right ventricular hypertrophy was present in 14 patients. Left ventricular strain pattern was present in 10 patients.

RADIOLOGICAL FEATURES

Cardiomegaly was present in all the 30 patients. It was mild in 12, moderate in 12, and severe in 6 patients; the cardiac silhouette seldom showed a distinct left or right ventricular contour. Left atrial enlargement was present in all the 30 patients. Post-stenotic dilatation of the aorta was present in 8 cases. The main pulmonary artery was dilated and prominent in 23 patients, but peripheral pruning of the pulmonary vessels was seen in 2 only. Dilated upper lobe veins were seen in 20 patients and in 8 of these there was hilar clouding; septal lines were present in 6 cases. Fluoroscopy revealed mitral valve calcification in 5 patients, but aortic valve calcification was not seen in any.

Table 4 *Electrocardiographic features*

	No. of patients	%
Sinus rhythm	21	69
Atrial fibrillation	9	31
Left and right atrial enlargement	4	13
Left atrial enlargement only	4	13
Left and right ventricular hypertrophy	4	13
Right ventricular hypertrophy only	2	6 6
Left ventricular hypertrophy only	10	33
Right axis deviation only	2	6 6

HAEMODYNAMIC FEATURES (Table 5)

Cardiac index varied from 1·4 to 4·2 l/min per m^2, and was low in 16 patients. Right atrial pressure was raised in 14 patients and conspicuously so (more than 10 mmHg mean pressure) in the 10 patients who were in congestive heart failure; three of these had a significant end-diastolic gradient (more than 3 mmHg) across the tricuspid valve when right atrial and right ventricular pressures were recorded simultaneously.

Nine patients had mild pulmonary hypertension (mean pulmonary artery pressure 25 to 50% of systemic pressure); 15 patients had moderate pulmonary hypertension (mean pulmonary artery pressure 50 to 75% of systemic pressure); 6 patients had severe pulmonary hypertension (mean pulmonary artery pressure more than 75% of systemic pressure), and 2 of these had systemic pressures in the pulmonary artery. Pulmonary vascular resistance was raised in 26 subjects (Table 5), and was more than 5 units in 18 patients. The mean direct or indirect left atrial pressure ranged from 14 to 45 mmHg; and was above 25 mmHg in 17 patients; direct left atrial pressure was below 15 mmHg in 2 patients, both of whom had a cardiac index below 2.0 l/min per m^2. The end-diastolic gradient across the mitral valve ranged from 8 to 35 mmHg; in 4 subjects it was less than 10 mmHg and in 14 above 20 mmHg. The peak-to-peak systolic gradient between left ventricle and aorta varied from 15 to 90 mmHg, and was less than 20 mmHg in one patient, between 20 and 50 mmHg in 19, and more than 50 mmHg in 10 patients. The three patients with the highest aortic systolic gradients (80, 90, and 130 mmHg) had relatively small end-diastolic gradients across the mitral valve (14, 14, and 20 mmHg).

CINEANGIOGRAPHIC FINDINGS

Left ventriculography showed a small cavity in 10 patients. A persistent intact crescent of the stenotic mitral valve in diastole was visible in 20 patients. Trivial mitral regurgitation was present in 6 patients (mild mitral regurgitation in 4). In all the 10 patients who had left atrial angiography, a persistent diastolic crescent of the mitral valve, persistent contrast gradient from the left atrium to left ventricle, and doming of the stenotic mitral valve were seen. Aortography showed a tricuspid aortic valve in all patients; aortic regurgitation of varying degree was present in 25 patients (trivial in 15 and mild in 10).

Discussion

The combination of aortic stenosis and mitral stenosis occurs in about 5 per cent of patients after rheumatic fever (Uricchio *et al.*, 1959; Katznelson *et al.*, 1960). The aortic stenosis usually makes its appearance 15 to 20 years after an episode of rheumatic carditis. Hence, rheumatic aortic stenosis is often diagnosed only in the fourth or fifth decade of life (Katznelson *et al.*, 1960; Honey, 1961; Zitnik *et al.*, 1965). In the younger age-group, aortic stenosis is usually considered congenital unless otherwise proved. Rheumatic aortic stenosis was diagnosed in our patients because of the history of rheumatic fever, the associated mitral stenosis, and the tricuspid aortic valve. A history of rheumatic fever was obtained in only 53 per cent of our patients with isolated mitral stenosis, while 93 per

Table 5 *Haemodynamic features*

Cardiac index (CI)	*l/min per m^2*	*No. of patients*	%
	<2·0	6	20
	2 0–2 8	10	33
	>2·8	14	47
Pulmonary vascular resistance	*Units × m^2**	*No. of patients*	%
	<3	4	13
	3–5	8	27
	5–10	14	47
	>10	4	13

*Pulmonary vascular resistance (PVR) expressed as arbitrary units, corrected for body surface area

$$PVR = \frac{P_{PA} - P_{LA}}{CI}$$

cent of this series gave a history of rheumatic fever. The more striking feature was the history of recurrent polyarthritis in 27 (90%) of these patients. A similar history was obtained in only 12 per cent with isolated rheumatic mitral stenosis (Cherian *et al.,* 1964). Pomerance (1972), in a study of 111 hearts from patients with aortic stenosis, did not find a single case of congenital aortic stenosis with a tricuspid valve. Similarly, Roberts (1970), in a study of the pathological anatomy of stenosed aortic valves, believed that it was reasonable to conclude that the aetiology was rheumatic when aortic stenosis with a tricuspid valve was associated with anatomical disease of the mitral valve. Calcification in rheumatic aortic valve stenosis is also said to be unusual and late, in contrast with congenital aortic stenosis (Aberdeen, 1969). Hence, we take the view that the aetiology of the aortic stenosis in our patients is rheumatic and not congenital.

The recognition of aortic stenosis in patients with mitral stenosis is not always easy (Katznelson *et al.,* 1960), but is important when selecting patients for closed valvotomy (Morrow *et al.,* 1962; Vytilingam *et al.,* 1964). The aortic systolic murmur in these patients is quieter and in 2 of our cases was absent. In 8 others admitted with congestive heart failure and low cardiac output, the aortic murmur was audible only after control of the cardiac failure and an increase in the cardiac output. Uricchio and Likoff (1957) and Honey (1961) have described patients with 'silent' aortic stenosis in whom, after mitral valvotomy, left ventricular enlargement and auscultatory features of aortic stenosis became obvious. Honey (1961) commented that in patients with combined aortic and mitral stenosis, the low cardiac output of severe mitral stenosis results in a low aortic valve gradient and only modest increases in left ventricular systolic pressure. This explains the rarity of left ventricular hypertrophy, angina, and post-stenotic dilatation of aorta in these patients. Moreover, the haemodynamic stresses on this deformed valve are less and, hence, calcification of the aortic valve also occurs rarely.

Development of severe mitral stenosis antedates that of aortic stenosis and the clinical picture is nearly always dominated by features of tight mitral stenosis and pulmonary hypertension. Two of our patients had closed mitral valvotomy performed 6 and 8 years before the present admission to hospital and aortic stenosis was not then detected clinically or at operation. We presume that this lesion developed later, concurrently with mitral restenosis.

Pulmonary hypertension has not been reported as a common sequel of this combination of valve lesions but 18 (60%) of our patients had significant rises in pulmonary vascular resistance (>5 units). Honey (1961), in a study of 35 patients with combined aortic stenosis and mitral stenosis, found only 5 patients (14%) with raised pulmonary vascular resistance. In the largest reported series with this combination (141 cases) the mean pulmonary artery pressures ranged from 25 to 32 mmHg and a marked elevation of mean pressure (40 mmHg or higher) was not observed. The pulmonary vascular resistance ranged from 1·4 to 5·8 units (Uricchio *et al.,* 1959). On the other hand, our patients were prone to develop pulmonary vascular disease at an early age, presumably as a result of the early development of important mitral stenosis.

The present study shows that rheumatic aortic stenosis, like rheumatic mitral stenosis, occurs at a much earlier age in Indian than in Western patients. The reasons for this are not clear. Apart from the different host and environmental factors, it is interesting that 27 of the 30 patients gave a history of recurrent migratory polyarthritis, while only 1 gave a history of a single episode.

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Left juxtaposition of the auricles with l-position of the aorta

Report of 6 cases

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Six hearts are described in which juxtaposition of the auricles to the left of the great arteries (left juxtaposition) was associated with l-position of the aorta. Atrial anatomy was abnormal but constant; the os of the right auricle occupied the expected site of the atrial septum, producing posterior and inferior displacement of this structure. This is of importance since the os could be mistaken for a defect of the atrial septum, while the displacement of actual defects is of significance to any intended catheterisation procedure including atrial septostomy. Five of the hearts showed atrioventricular concordance while the other specimen was an example of primitive ventricle with a right-sided outlet chamber. The ventriculoarterial connection in this latter case was normal, with l-malposition (anatomically corrected malposition). Ventriculoarterial connections in the other hearts were transposition in 3, single aortic trunk with pulmonary atresia in 1, and an intermediate between double outlet right ventricle and transposition in the other. These cases confirm the observation that juxtaposition of the auricles is associated with severe cyanotic congenital heart disease.

In the normal heart the auricular appendages (auricles) extend forwards from the atria to encircle the origin of the aorta and pulmonary artery. The uncommon condition in which the auricles lie side by side, either to the left or the right of the great arteries, has been well recognised since the description of a single case by Birmingham (1893). This anatomical arrangement was called juxtaposition of the atrial appendages by Dixon (1954) and is well known to be associated with major intracardiac anomalies with cyanosis, particularly when the right auricle is juxtaposed to the left (Melhuish and Van Praagh, 1968).

Six hearts with left juxtaposition of the auricles are described, in each of which the aortic valve is situated to the left of the pulmonary valve in situs solitus individuals with atrioventricular concordance. The hearts show a range of malformations at ventricular and conal levels. The atrial anatomy, however, was in all cases relatively constant. As it has been shown that juxtaposition of the auricles is readily identified radiologically (Ellis and Jameson, 1963), a thorough understanding of the likely accompanying defects may facilitate treatment.

The cases

The 6 hearts were from the collections of necropsied material of the Royal Postgraduate Medical School, the Hospital for Sick Children, and the Cardiothoracic Institute, all in London (Table). All had been hospital patients. Cases 3 and 6 had undergone aorto-pulmonary arterial (Waterston) anastomosis, and case 5 had had an atrial baffle (Mustard) operation. The remaining 3 had had no operation. All 6 patients had died of causes related to their malformations. Their ages ranged from 5 days to 30 years.

Anatomical findings

All 6 specimens had situs solitus viscero-atrial relations, and all had concordant atrioventricular connections. In each case the right auricle was to the left of the great arteries, so that it lay superior and slightly anterior to the left auricle (Fig. 1). The aorta

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Table *Anatomical findings in 6 patients with {S-D-L} segmental anatomy and left juxtaposition of auricles*

No.	*Age*	*Sex*	*Situs*	*Cardiac segments**	*PFO*	*ASD I*	*ASD II*	*VSD*	*Origin of PA*	*RV*	*Origin of aorta*	*Conus*	*Pulmonary outflow tract obstruction*
1	3/12	M	Solitus	S-D-L	+	0	0	Ant	RV-LV	N	RV	Aortic	0
2	16	F	Solitus	S-D-L	0	0	+	Post	LV	H	RV	Bilat	0
3	5d	F	Solitus	S-D-L	+	0	0	Ant	0	N	RV	Aortic	Atresia
4	30	F	Solitus	S-D-L	+	0	+	VBF	Outlet chamber	O-C	Ventricle	Bilat	0
5	4/12	M	Solitus	S-D-L	0	+	0	Ant	LV	H	RV	Aortic	AMS
6	3/12	M	Solitus	S-D-L	+	0	+	Post	LV	H	RV	Aortic	Fibrous

Abbreviations: A, aortic; Ant, anterior; AMS, aneurysm of membranous septum; ASD I, primum atrial septal defect; ASD II, secundum atrial septal defect; AV-SLV, atrioventricular valve—semilunar valve continuity; Bilat, bilateral; DORV, double outlet right ventricle; H, hypoplastic; LV, left ventricle; M, mitral; N, normal; O-C, outlet chamber; P, pulmonary; PA, pulmonary artery; PDA, persistent ductus arteriosus; PFO, patent foramen ovale; Post, posterior; PS, pulmonary stenosis; RV, right ventricle; SVC, superior vena cava; T, tricuspid; TGA, transposition of great arteries; VBF, ventriculobulbar foramen.
*According to the classification of Melhuish and Van Praagh (1968).

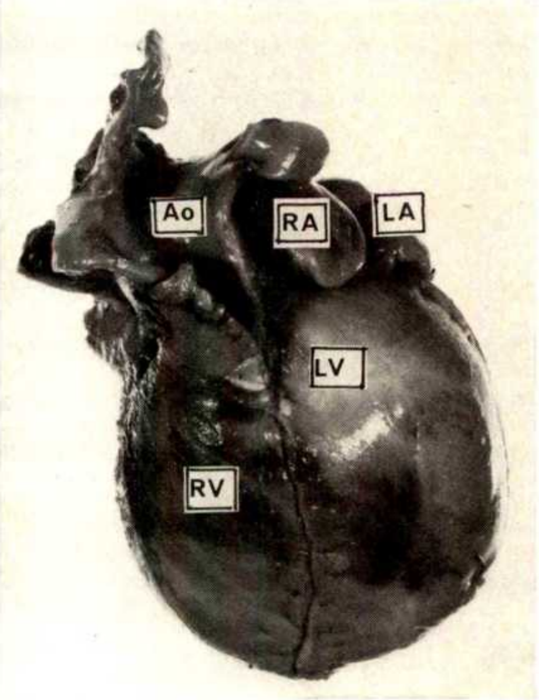

Fig. 1 *Case 3. The right auricle (RA) is to the left of the great arteries, and lies anterior and slightly superior to the left auricle (LA). The aorta (Ao) is anterior and to the left of the atretic pulmonary artery. (RV=right ventricle; LV=left ventricle.)*

in each case was anterior and to the left of the main pulmonary artery, so that the segmental anatomy for the whole group was {S-D-L} (Fig. 2). In specimens 1 and 6 the apex of the heart was directed to the right, and in the remaining 4, the apex was to the left.

ANATOMY OF ATRIA

Although the atria received their appropriate veins, the chambers were not normally related to one another. The left atrium was posterior to the right atrium, as is usual, but the right atrium, instead of forming the right border of the heart, was immediately anterior to the left. The position and relations of the left atrium and its auricle were not deranged by juxtaposition of the right auricle. The right auricle in all cases was displaced behind the great arteries, the atrium itself remaining as a right-sided chamber. The os of the right auricle was anterior to the crista terminalis, so that at first sight it resembled a defect of the atrial septum. Defects of the atrial septum were situated posteriorly in the chamber (Fig. 3).

In heart 1, the superior vena cava entered the right atrium more inferiorly than is usual, and the foramen ovale was patent. The atrium in heart 2 received the superior and inferior venae cavae in the normal manner, and there was a large persistent left superior vena cava (Fig. 2) in addition to a channel resembling the normal coronary sinus, which received the great cardiac vein. There was a secundum defect of the atrial septum, 29 mm in diameter. Indeed, in this heart, the septum primum was represented only by a rim of tissue, 2 mm high, on the inferior aspect of the defect. Heart 3 had a

AV-SLV continuity	*Coronary arteries*	*Additional data*	*Anatomical diagnosis*
P-M-T	TGA	Apex of heart to right	Transitional DORV-TGA without PS
None	Single	Left SVC	TGA; hypoplastic RV
None	TGA	PDA	Solitary aortic trunk
None	Single	0	Primitive ventricle; anatomically corrected malposition
P-M-T	TGA	PDA	TGA; subpulmonary stenosis resulting from AMS; hypoplastic RV
P-A-T-M	TGA	PDA; apex of heart to right	TGA; valvar and subvalvar pulmonary stenosis; hypoplastic RV

stretched superior foramen ovale. Heart 4, which weighed 870 g, had 2 secundum defects; the larger, in the inferoanterior portion of the septum primum measured 40 × 25 mm, and the smaller defect, in the superior posterior septum, measured 6 mm in diameter. Heart 5 had an endocardial cushion defect, the atrial component of which was large; accurate assessment of its size was not possible because of the surgically placed baffle. Heart 6 had a superior foramen ovale. In this heart the atrial septum lay in a more oblique plane, so that it more closely resembled the normal atrial septum than in the other 5 cases. The foramen ovale was patent superiorly, and because of the orientation of the atrial septum in this heart, constituted a communication between the right auricle and the left atrium.

ANATOMY OF VENTRICLES

All the specimens except heart 4 had two identifiable ventricular chambers. Two atrioventricular valves were recognised in each case, and all the hearts had ventricular septal defects which permitted intracardiac shunting.

In heart 1, the ventricular septal defect (14 × 10 mm) was high in the anterior ventricular septum; the trabecula septomarginalis formed its floor and the defect extended posteriorly to the atrioventricular valves which made contact through its posterior margin. Both aortic and pulmonary valves were related to the defect, the pulmonary valve exactly overriding the septum (Fig. 4).

Heart 2 had a dysplastic tricuspid valve, right ventricle, and aorta. The ventricular septal defect occupied the posterior septum and was subpulmonary (Fig. 5). Its topography resembled an endocardial cushion defect, so that the tricuspid valve marked the superior boundary. The tricuspid and mitral valves were in continuity through the defect.

In heart 3 the ventricles were of equal size. The defect, 10 × 10 mm, lay immediately beneath the aortic valve, anterior to the septomarginal trabecula (Fig. 6). There was no pulmonary valve.

In heart 4 (Fig. 7A), both atrioventricular valves opened into a primitive ventricle. The aorta arose from the ventricle, and the pulmonary artery originated from a bulbar (outflow) chamber which communicated with the primitive ventricle through a ventriculobulbar foramen (Fig. 7B).

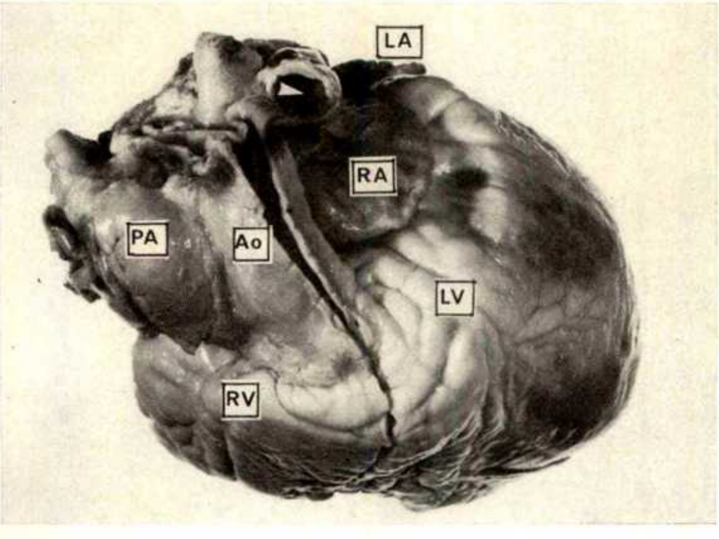

Fig. 2 *Case 2. The aorta (Ao) arises from the right ventricle (RV) and is placed anteriorly and to the left of the pulmonary artery (PA). LA = left auricle; LV = left ventricle. The persistent left superior vena cava is arrowed in white.*

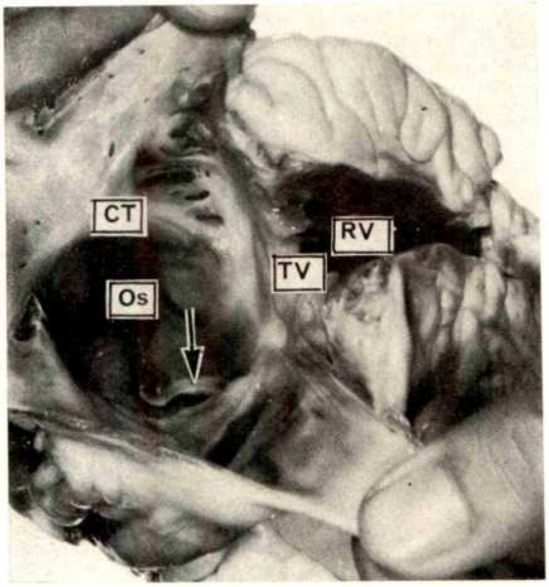

Fig. 3 *Case 2. The right atrium and right ventricle (RV) are hypoplastic. The septum primum (arrowed) is seen as a rim of tissue 2 mm in depth. The os of the right auricle (Os) appears at first sight to be a defect of the atrial septum. CT = crista terminalis; TV = tricuspid valve.*

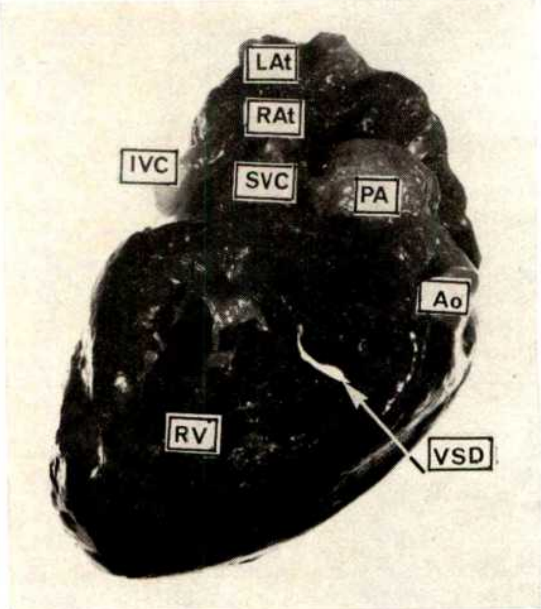

Fig. 4 *Case 1. This specimen is a waxed preparation, thus the photograph appears rather dark. The defect of the ventricular septum (VSD) is seen as a slit in this view, and the pulmonary artery (PA) overrides it. The aorta (Ao) arises wholly from the right ventricle (RV). The great arteries are equal in size. IVC = inferior vena cava; LAt = left atrium; RAt = right atrium; SVC = superior vena cava.*

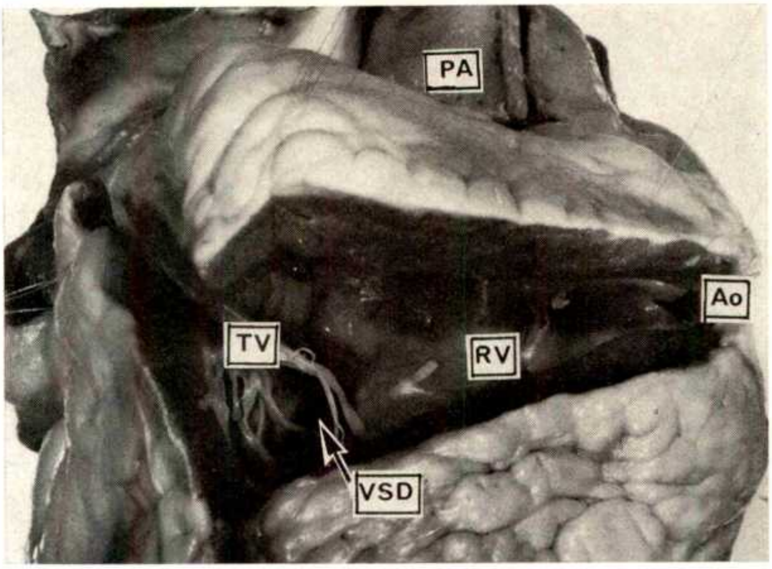

Fig. 5 *Case 2. The defect of the ventricular septum (VSD) is posterior. The tricuspid valve (TV), right ventricle (RV), and aorta (Ao) are hypoplastic.*

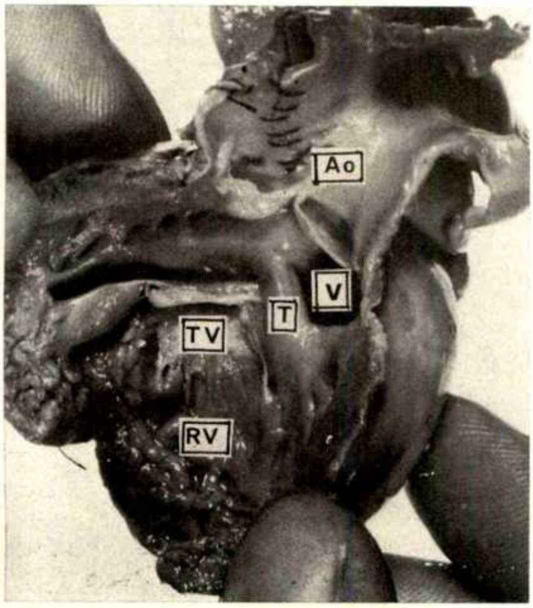

Fig. 6 *Case 3. The defect of the ventricular septum (V) is anterior to the trabecula septomarginalis (T), and is subaortic. Other abbreviations as in previous figures.*

Heart 5 had hypoplasia of the tricuspid valve and the right ventricle. The ventricular septal defect was anterior to the trabecula septomarginalis and in the subaortic position (Fig. 8A and B).

Heart 6 also had a hypoplastic tricuspid valve and right ventricle, which was divided into discrete inflow and outflow portions by anomalous muscle bands. The defect in this specimen was midseptal, lying beneath the pulmonary outflow tract, but extended to the posterior ventricular septum (Fig. 9A and B).

ANATOMY OF CONUS

Ventriculoarterial connections were abnormal in all 6 specimens, and the conal anatomy differed widely. In heart 1, the aorta arose from a muscular conus in the right ventricle. The pulmonary artery, separated from the aorta by the conus septum, overrode the ventricular septal defect so that the pulmonary valve was in fibrous continuity through the defect with both the atrioventricular valves. The ventriculoarterial connection was transitional between that of double outlet right ventricle and transposition.

In heart 2, the aorta arose from a muscular right ventricular conus. The pulmonary artery arose ex-

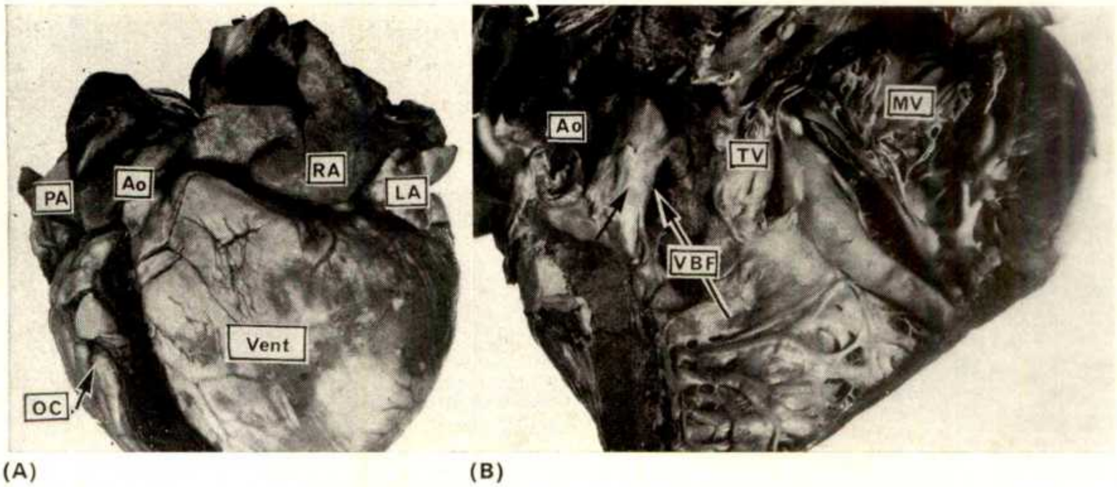

Fig. 7 *Case 4. (A) Showing the juxtaposed auricles (RA, LA). The great arteries (PA, Ao) are equal in size. The wall of the right atrium is hypertrophied. OC=outlet chamber; Vent=ventricle. (B) The ventricular morphology of this heart is that of primitive (single) ventricle with an outlet chamber. The illustration shows the primitive ventricle from which the aorta (Ao) arises, the ventriculobulbar foramen (VBF), and the two atrioventricular valves (TV, MV). The pulmonary artery is not seen, but arises from the outlet chamber. There are numerous patches of fibrosis ('jet lesions') especially on the bulbar septum (arrowed in black). In this heart, therefore, the great arteries are normally connected, but show l-malposition (anatomically corrected malposition). Note that both the tricuspid and mitral valves open to the primitive ventricular chamber, and are separated by a prominent posterior ridge. Note also that the aortic valve is supported by a complete muscular conus.*

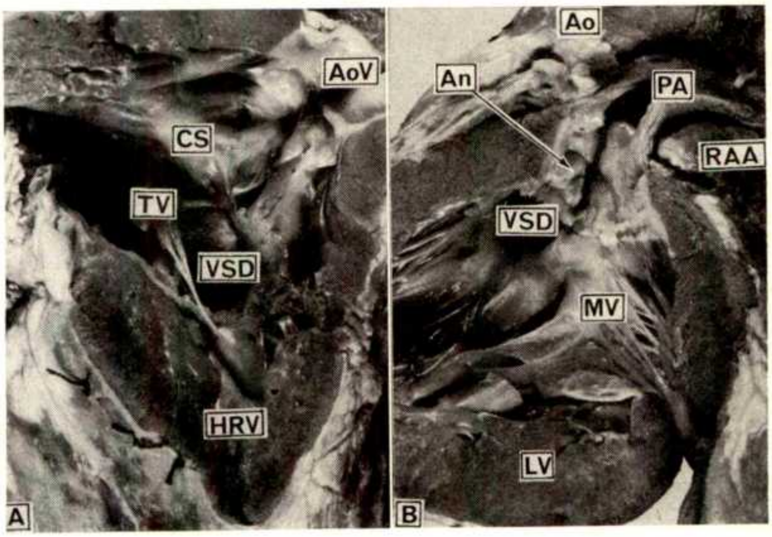

Fig. 8 *Case 5. (A) The tricuspid valve (TV) and right ventricle (HRV) are hypoplastic. This child had an atrioventricular canal, the ventricular component of which (VSD) is anterior to the trabecula septomarginalis, and subaortic. AoV = aortic valve; CS = conus septum. (B) The left side of the heart of case 5. The right auricle (RAA) is seen to the left of the pulmonary artery (PA). The mitral (MV) and pulmonary valves are in fibrous continuity. The membranous septum is aneurysmal (An) and causes a degree of obstruction to the pulmonary outflow tract. LV = left ventricle.*

clusively from the left ventricle, but was dissociated from the mitral valve by a slender muscle slip, not more than 2 mm in width; this muscle slip extended from the left ventricle into the posterior conus septum, so that neither the aortic nor the pulmonary valve was in fibrous continuity with either atrioventricular valve. The atrioventricular valves, however, were continuous with one another through the defect in the ventricular septum. The ventriculoarterial connection was that of transposition. In heart 3, the aorta arose from a muscular conus, immediately above the septal defect. The atretic pulmonary artery was represented by a thread of tissue and did not make contact with either ventricle. There was thus no fibrous continuity with either atrioventricular valve. Since we were unable to identify the origin of the pulmonary artery, the ventriculoarterial connection was described as single aortic trunk arising from the right ventricle with l-malposition.

Heart 4 had bilateral muscular conus. The atrioventricular valves were widely separated by muscle from the aorta, and the pulmonary artery arose from the bulbar (outflow) chamber. In this heart the ven-

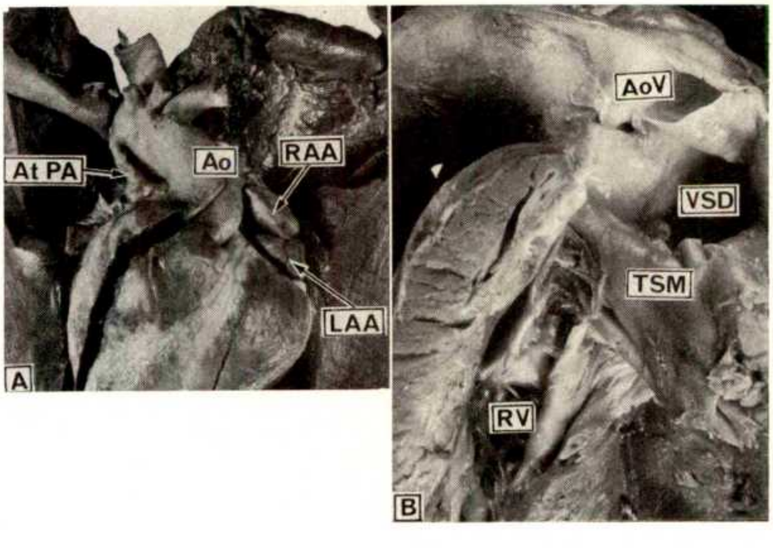

Fig. 9 *Case 6. (A) The apex of the heart is directed to the right. The right auricle (RAA) lies superior and anterior to the left auricle (LAA). The aorta (Ao) is to the left of the atretic pulmonary artery (At PA). (B) The right ventricle (RV) in heart 6. The chamber is divided by anomalous muscle bands into discrete inflow and outflow portions. The ventricular septal defect (VSD) is midseptal, superior to the trabecula septomarginalis (TSM), and extends to the posterior part of the ventricular septum. AoV = aortic valve.*

triculoarterial connections were normal but l-malposition was present; this is usually termed 'anatomically corrected malposition'.

Heart 5 had a subaortic conus only, and the pulmonary valve arising from the left ventricle was in fibrous continuity with both atrioventricular valves. The ventriculoarterial connection was that of transposition. In heart 6 there was continuity between the aortic and pulmonary valves, resulting from the defect in the conus septum, and fibrous subpulmonary obstruction permitted continuity with the mitral and tricuspid valves. The muscular conus, however, was subaortic. The ventriculoarterial connection was that of transposition.

OBSTRUCTION TO PULMONARY OUTFLOW TRACT

One of the 6 patients (case 3) had atresia of the pulmonary artery. The main pulmonary artery was represented by a thread-like structure which made no connection with either ventricle, nor was a pulmonary valve present in either ventricle.

Pulmonary outflow tract obstruction was present in hearts 5 and 6. In heart 5, the left ventricular outflow tract was obstructed by an aneurysmal partly formed membranous septum (Fig. 9B), but the pulmonary valve was not stenotic. Heart 6 had an imperforate, small pulmonary valve deeply wedged between the two atrioventricular valves. Additional obstruction was caused by fibrosis and fibrous excrescences of the inferior portion of the conus septum which was displaced posteriorly; these excrescences resembled valve tissue.

DISTRIBUTION OF CORONARY ARTERIES

Hearts 1, 3, 5, and 6 all had a coronary artery distribution consistent with concordant transposition in situs solitus. The non-coronary sinus of the aortic valve was anteromedial, and the anterior descending and circumflex arteries arose from a common artery from the posterolateral aortic sinus. The anterior descending artery followed the interventricular sulcus, giving off septal and muscular branches, and the circumflex coronary artery arose from the main stem to pass posteriorly in the left atrioventricular groove. The right coronary artery originated from an ostium in the posteromedial aortic sinus, and followed the right atrioventricular groove; numerous conal branches arose from the right coronary artery which terminated as the posterior descending coronary artery.

Hearts 2 and 4 both had a single coronary artery arising from an ostium in the anteromedial aortic sinus. The distribution of the artery was identical in the two hearts, except for some small marginal branches. The coronary artery bifurcated about 1 cm from its origin to give rise to a large artery which lay in the right atrioventricular groove; a number of marginal and diagonal arteries arose from it and the artery terminated as a posterior descending artery on the diaphragmatic surface of the heart. The smaller, left hand branch of the single coronary artery had the appearance of a large conal coronary artery and gave origin to a slender branch in the left atrioventricular groove; the conal portion of the artery divided into numerous small branches which fanned widely over the left ventricle.

Discussion

The anatomical features of 6 hearts with left juxtaposition of the auricles and l-position of the aorta have been described. In addition to these common features, situs solitus and atrioventricular concordance were present in each case. The atrial anatomy was relatively constant, but the hearts showed considerable variation in ventricular and conal anatomy.

ATRIAL ANATOMY IN LEFT JUXTAPOSITION OF AURICLES

Both systemic and pulmonary venous drainage was normal in all 6 hearts; in case 2, the persistent left superior vena cava opened into the right atrium. The unusual feature of this case with left superior vena cava was that a great cardiac vein resembling a 'coronary sinus' also drained into the right atrium. The coronary sinus is the original left sinus horn, and the left superior vena cava normally regresses, persisting as the oblique vein of Marshall. The posterior great cardiac vein normally drains into the left sinus horn. In heart 2 both the left sinus horn and the great cardiac vein were present as separate channels. This finding was noted in 4 of 28 cases of left juxtaposition reviewed by Puech *et al.* (1966) who added one in their series of 3 cases. Melhuish and Van Praagh (1968) noted the same feature in 2 of 21 cases of juxtaposition of the auricles, and Rosenquist *et al.* (1974) described it in one of 6 hearts with left auricular juxtaposition.

An interatrial communication was present in all 6 hearts, and, where this communication was the result of patency of the foramen ovale, this patency occurred in the superior aspect of the fossa ovalis. Rashkind septostomy had been attempted in case 6, but was unsuccessful. The plane of the atrial septum and the anatomy of the fossa ovalis in this condition makes septostomy difficult. This procedure has failed even when the juxtaposition was recognised (Tyrrell and Moes, 1971). We suggest, on anatomical premises, that balloon septostomy may be practicable in this condition if the tip of the catheter is directed superiorly as well as posteriorly, as the valve of the foramen ovale is a superior structure in left juxtaposition of the auricles.

L-POSITION OF AORTA

The majority of hearts with left juxtaposition of the auricles exhibit d-position of the aorta {S-D-D} (Melhuish and Van Praagh, 1968) but a significant proportion have l-position of the aorta. {S-D-L} segmental anatomy has been reported in association with left juxtaposition by Melhuish and Van Praagh (1968), Wagner *et al.* (1970), Charuzi *et al.* (1973), and Lincoln *et al.* (1975). From the published reports, together with our series, {S-D-L} segmental anatomy appears to be present in about 30 per cent of cases with left juxtaposition.

Three of the 6 hearts (2, 5, and 6) showed complete l-transposition (solitus-concordance-l-transposition). An anterior, subaortic ventricular septal defect was present in heart 5, and all 3 had hypoplasia of the tricuspid valve, the right ventricle, and the aorta.

Heart 1 represented a transitional stage between double outlet right ventricle and complete transposition. If double outlet ventricle is defined as that condition in which 1½ great arteries or more arise from the same ventricle (Lev *et al.*, 1972), this heart arbitrarily could be placed into either category. Transitional hearts have been described by Lev *et al.* (1972) and Anderson *et al.* (1974), but we are unaware of another report of association with left juxtaposition. If this heart, without pulmonary stenosis, is classified as double outlet right ventricle with {S-D-L} segmental anatomy, this is the ninth such case described, others having been reported by Hallermann *et al.* (1970), de la Cruz *et al.* (1974), and Van Praagh *et al.* (1975a, b).

Heart 3 had pulmonary atresia, but the ventricular origin of the pulmonary artery could not be identified so that it was not appropriate to classify this as a case of transposition. We strongly support the view of Van Praagh *et al.* (1971) that for transposition to exist, both great arteries must be placed across the ventricular septum to originate from morphologically inappropriate ventricles. Where only one great artery is present, it is unrewarding to speculate on the ventricular origin of the other.

Heart 4 showed anatomically corrected malposition associated with a primitive ventricle. Anatomically corrected malposition is rare, and has not, as far as we are aware, been reported previously in association with a primitive ventricle. Freedom and Harrington (1974) reviewed 13 cases of anatomically corrected malposition of which 7 had left juxtaposition of the atrial appendages, and Anderson *et al.* (1974b) described 4 cases, of which 2 had juxtaposition. Of these 4, 3 had a single coronary artery with identical distribution to that of the present case.

SURGICAL IMPLICATIONS

The coexistence of {S-D-L} cardiac segmental anatomy with cyanotic congenital heart disease does not preclude surgical treatment (Van Praagh *et al.*, 1975a, b), but the variations in anatomy at both ventricular and conal levels necessitate careful assessment of the intracardiac arrangements.

The 3 hearts in the present series with transposition all had hypoplastic right ventricles. A Mustard operation had been performed in case 5, but the patch had narrowed the already small tricuspid valve; the defect of the posterior ventricular septum was patent, and there was considerable obstruction to the outflow tract of the left ventricle. The implications of juxtaposition in relation to Mustard's operation have recently been discussed in detail by Rosenquist *et al.* (1974) and Urban *et al.* (1976). Heart 6 also had subpulmonary obstruction, while case 2, with a subpulmonary ventricular septal defect, had severe pulmonary vascular disease.

Hearts 2 and 4 each had a single coronary artery, the distribution of which could prejudice surgical incision in such hearts. We support the view that opacification of the coronary arteries in patients with l-position of the aorta is a valuable aid to the determination of ventricular morphology, as the coronary arteries have the distribution appropriate to their ventricles (Van Praagh *et al.*, 1975b; Allwork *et al.*, 1976).

EMBRYOLOGICAL CONSIDERATIONS

The genesis of the ventricular and conal abnormalities described here has been discussed extensively in recent years (Van Mierop *et al.*, 1963; Van Mierop and Wiglesworth, 1963; Van Mierop, 1971; Van Praagh, 1971; Anderson *et al.*, 1974; Allwork, 1975, 1976), but the reports concerning the atrial anomalies are less numerous. In particular, the morphogenesis of juxtaposition of the auricles is obscure.

Wenner (1909) considered that juxtaposition of the auricles resulted from 'insufficient torsion' of the primitive heart tube. Dixon (1954) accepted this 'explanation' as did Los (1968). Melhuish and Van Praagh (1968) proposed that the condition was mainly the result of an arrest of normal development, and that juxtaposition was an effect, rather than a cause. While our findings are in accord with those of the last-named authors with respect to the range of ventricular and conal anomalies associated with juxtaposition, we are unable to accept that the *auricles* are ever juxtaposed in normal development.

The auricles of the atria are trabeculated muscular structures, macroscopically quite distinct from the smooth walled segments. The auricles are derivatives of the primitive atrium, which at 20 days of gestational age is a single chamber, and part of the primitive heart tube. The smooth walled segments of the definitive atria are derived from the primitive sinus venosus and the pulmonary veins (Boyd, 1965). The primitive sinus venosus receives bilaterally both the vitelline and umbilical veins, together with the common cardinal vein. It is incorporated into the primitive atrium to form a single chamber at about 25 days of gestational age (Boyd, 1965; Hamilton and Mossman, 1972). This common chamber then expands ventrally (anteriorly) and transversely, so that in normal development, the atrium is well seen on either side of the bulbus cordis, by which it is indented. The ventro- (antero-) lateral extremities of the primitive atrium differentiate into the characteristic left and right auricles.

At about 26 days of gestation, the primitive atrium, still a single chamber, opens into the primitive ventricle. The only route for the circulation is from the atrium to the ventricle, through the ventriculobulbar foramen to the bulbar chamber thence to the septating outflow tract. From this account, it is clear that the route from atrium to ventricle is left sided, but we are unaware of any description of normal development which suggests that the extremities of the atria are both left sided.

In normal development the atrioventricular canal gains direct access to the bulbus cordis by a lateral expansion, and the primitive atrioventricular canal is divided into the left and right atrioventricular canals (the future atrioventricular valve orifices) by the endocardial cushions (Boyd, 1965; Los, 1968; Hamilton and Mossman, 1972; Anderson and Ashley, 1974). The immediate cause of the lateral expansion of the atrioventricular canal is a controversial topic but there is general agreement that the process is bound up with the expansion of the elements which will contribute to the definitive right ventricle.

The obvious feature of the 6 hearts presently described is that, in general, the right side of the ventricular segment of the heart is underdeveloped (hearts 2, 4, 5, and 6). Specimen 4 represents an adult example of the route taken by the circulation in the fourth week of gestation. None of the explanations for the morphogenic processes which result in the anomalies described here is very satisfactory. If juxtaposition resulted merely from failure of the atrioventricular canal to expand to the right, the fairly frequent observation of {S-D-L} segmental anatomy (about 30% of cases) would be hard to explain, as would the relative frequency of anterior defects of the ventricular septum. That rightwards expansion of the primitive atrioventricular canal *has* failed is self evident in view of the high incidence of underdevelopment of the right side of the heart. Hypoplasia of the right heart cannot by itself explain the fact that in 5 of our 6 cases the aorta originated in the right ventricle, nor can it explain the l-position of the aortic valve relative to the pulmonary valve in every case. It is possible that the abnormal atrial interrelation is the result of abnormal development *ab initio* of the venous end of the heart coupled with inadequate morphogenic movements. We suggest, therefore, that the developmental events leading to the formation of hearts such as the 6 described are a great deal more complex than has previously been considered.

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Addendum

Since completing this report, S.P.A. has seen an example of right juxtaposition of the auricles. The patient was a girl of 15. The anatomical findings were situs solitus, common atrium, primitive ventricle with two atrioventricular valves (the left rather small). The aorta arose anteriorly from the main chamber, and a left sided outlet chamber, obstructed by muscle, gave rise to a small pulmonary artery. There were two coronary arteries. Operation to septate the ventricle and atrium and to enlarge the pulmonary outflow tract by a gusset was performed by Professor H. H. Bentall at Hammersmith Hospital in November. The girl has made an excellent recovery. With the exception of pulmonary outflow tract obstruction in this patient, the anatomy is essentially similar to that of heart 4 described above. The ventriculoarterial connection is that of normal connections with d-malposition. This finding of complex congenital malformations with abnormal position of the great arteries confirms the previous findings of Anderson *et al.* (1976) in right juxtaposition of the auricles.

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Clinical and electrophysiological effects of intravenous quinidine in man[1]

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Quinidine gluconate (total dose 4·4 to 9·1 mg/kg) was infused intravenously over 22 minutes in 20 patients with either frequent premature ventricular contractions or supraventricular arrhythmias, 16 of whom had bundle-branch block. Therapeutic plasma quinidine levels (3 to 7 mg/l) were achieved in 15. Heart rate, atrioventricular nodal, and infranodal conduction times did not change significantly. The QRS duration increased significantly from 128±30 to 134±29 ms at peak plasma quinidine levels (P < 0·01). Mild hypotension occurred during infusion in most patients. Two patients had a severe but transient toxic response characterised by hypotension, nausea, vomiting, and diaphoresis. Atrioventricular dissociation with escape His bundle or fascicular rhythm occurred in 1 patient with sinus bradycardia. Bundle-branch block does not contraindicate administration of quinidine. Quinidine gluconate administered intravenously (0·3 to 0·4 mg/kg per min) is frequently associated with hypotension and should be used only in an intensive care setting and with careful monitoring of blood pressure.

Oral administration of quinidine has proved to be effective and safe for the control of atrial and ventricular arrhythmias provided that plasma levels are kept within the therapeutic range (Sokolow and Ball, 1956), whereas the intravenous use of quinidine has been associated with serious untoward reactions (Armbrust and Levine, 1950; Chapman, 1945; Hepburn and Rykert, 1937; Riseman and Linenthal, 1941; Strong and Munroe, 1940) and is generally considered to be contraindicated (Selzer, 1972). Quinidine delays conduction and increases refractoriness of the His-Purkinje system and slows conduction in ventricular muscle. Because of these actions, quinidine is believed by some to be relatively contraindicated in patients with bundle-branch block (Sokolow and Perloff, 1961). In the study reported here, we attempted to correlate the electrophysiological effects of quinidine on atrioventricular and intraventricular conduction with plasma drug levels in patients with bundle-branch block in an effort to define a rate of intravenous administration of this drug in man which yields therapeutic blood levels within a relatively short period of time but without undue toxic effects.

Subjects and methods

Twenty patients with either frequent premature ventricular contractions or supraventricular arrhythmias in whom prolonged therapy with oral quinidine was anticipated were studied. Informed consent was obtained and the study conducted in accordance with a protocol approved by the Committee on Human Experimentation of the University of California, San Francisco. No patient was receiving other antiarrhythmic agents at the time of the study. A hexapolar electrode catheter was introduced percutaneously via the right femoral vein, and His bundle recordings were obtained by previously described techniques (Damato *et al.*, 1969; Scheinman *et al.*, 1973). External scalar leads X, Y, and inverse Z of the Frank orthogonal system were recorded simultaneously with the His bundle electrogram at a paper speed of 100 mm/s. The atrioventricular nodal conduction time (AH interval) was measured from the earliest rapid deflection of the atrial electrogram to the initial deflection of the His bundle depolarisation. The conduction time from bundle to ventricle (HQ interval)

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[2] This study was performed during tenure of the American Heart Association Teaching Scholar in Cardiology.

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was measured from the initial His deflection to the earliest onset of ventricular depolarisation recorded on the external leads; the onset of the V deflection in the His bundle recordings was not used.

Preliminary studies showed that infusion of less than 3 mg/kg body weight over 22 minutes failed to produce therapeutic blood levels of quinidine (3 to 7 mg/l). In the present study, quinidine gluconate was diluted in 50 ml 5 per cent dextrose in water and administered over 22 minutes by a Harvard constant infusion pump to provide a total dose of from 4·4 to 9·1 mg/kg quinidine gluconate (average 6·9) at infusion rates of 0·20 to 0·45 mg/kg per min (average 0·34). Blood specimens for quinidine assay were withdrawn every 5 minutes during infusion and for 20 minutes afterwards from a polyethylene catheter inserted into a vein in the opposite arm. Simultaneously with withdrawal of blood specimens, the systemic blood pressure was measured by the cuff method, the His bundle electrogram recorded, and 30 second electrocardiographic recordings were obtained in order to count premature beats. Patients were observed closely and asked to report any symptoms during the study.

Plasma quinidine levels were measured by two techniques: (1) a standard colorimetric method involving alkaline extraction into ethylene chloride (Brodie *et al.*, 1946), and (2) a more specific extraction procedure coupled to a thin layer chromatography separation (Ueda *et al.*, 1976). Plasma quididine levels are expressed as mg/l of quinidine base. Where applicable, the data were analysed using Student's paired t test.

Results

Pertinent clinical information, peak plasma quinidine levels, and electrophysiological data for each patient are summarised in Tables 1 and 2. Twelve patients manifested either left bundle-branch block, right bundle-branch block with left anterior fascicular block, or right bundle-branch block with left posterior fascicular block; of these, 8 had prolonged HQ intervals (>55 ms). Four patients had right bundle-branch block alone or isolated left anterior fascicular block; of these, one had a prolonged HQ interval. Four had no intraventricular conduction abnormality; of these, one had a slightly prolonged HQ interval (58 ms). Of the 20 patients, 13 had premature beats at the time of the study.

Plasma quinidine levels tended to increase progressively during infusion, and in all but one patient the peak quinidine level was achieved at the end of the infusion (Fig. 1). Therapeutic plasma quinidine levels were achieved (3 to 7 mg/ml) when the infusion was stopped in 15 patients. There was no significant difference in plasma quinidine levels determined by the colorimetric assay and the more specific chromatographic technique. Values referred

Table 1 *Pertinent clinical and electrocardiographic data and amount of quinidine administered*

Case No.	*Cardiac disease*	*CHF*	*Conduction disturbance*	*Arrhythmia*	*Amount quinidine infused (mg/kg)*	*Peak quinidine plasma level (mg/l)*
1	CAD	Yes	LAHB	PVC	7·5	3·1
2	CAD	Yes	LAHB, RBBB	PVC	7·1	4·9
3	CAD	Yes	LBBB	PAC	7·2	3·5
4	CAD	Yes	LAHB	PVC	9·1	4·3
5	CAD	Yes	RBBB	PVC	5·4	3·3
6	CAD	No	None	PVC	9·0	8·4
7	Cardiomyopathy	Yes	LPHB, RBBB	PVC	6·7	0·8
8	RHD	Yes	LBBB, SB	PAT*	7·3	5·8
9	Unknown	No	None	PVC	4·6	1·4
10	Unknown	No	LAHB, RBBB	PAC	5·8	4·6
11	Cardiomyopathy	Yes	LAHB, SB	PJC	6·6	4·1
12	Unknown	No	LBBB	PAC	7·4	3·0
13	CAD	No	None	PAT*	9·0	4·0
14	HHD	Yes	None	Atrial flutter	8·8	5·8
15	CAD	No	LPHB, RBBB	PVC	9·0	2·9
16	CAD	Yes	LBBB	PVC	5·4	5·3
17	HHD	Yes	LBBB	PVC	7·2	2·8
18	Unknown	Yes	LAHB, RBBB	PVC	5·2	3·7
19	Cardiomyopathy	No	LAHB, RBBB	PVC, PAC	6·0	1·6
20	Unknown	Yes	LBBB	PVC, PAC	4·4	3·2
Mean ±SD					6·9 ±1·5	3·8 ±1·7

CHF, congestive heart failure; CAD, coronary artery disease; RHD, rheumatic heart disease; HHD, hypertensive heart disease; LAHB, left anterior hemiblock; RBBB, right bundle-branch block; LBBB, left bundle-branch block; LPHB, left posterior hemiblock; SB, sinus bradycardia; PAC, premature atrial contractions; PVC, premature ventricular contractions; PAT, paroxysmal atrial tachycardia; PJC, premature junctional contractions.
*Not at time of study.

Table 2 *Blood pressure and electrophysiological intervals before administration of quinidine and at peak plasma quinidine level*

Case No.			*Intervals (ms)*							
	Blood pressure (mmHg)		*RR*		*AH*		*HQ*		*QRS*	
	Before	*Peak*	*Before*	*Peak*	*Before*	*Peak*	*Before*	*Peak*	*Before*	*Peak*
1	130/80	110/76	780	750	105	105	40	45	105	125
2	180/80	160/70	885	1000	105	105	45	50	135	145
3	170/70	160/60	730	750	100	90	65	65	140	140
4	120/80	90/55	810	700	120	115	45	45	100	100
5	135/90	115/70	580	600	90	85	95	100	110	110
6	110/70	90/60	600	640	90	85	58	65	105	135
7	120/70	80/50	820	870	75	80	80	70	170	180
8	110/60	105/60	1070	1120	75	80	80	60	155	170
9	120/85	80/60	880	720	80	50	45	50	80	80
10	170/105	110/60	850	780	80	80	60	60	125	135
11	110/70	80/50	1015	1100	190	180	50	50	100	120
12	114/72	102/64	720	670	80	75	55	65	145	160
13	110/85	90/70	740	650	60	60	45	50	70	80
14	200/90	165/90	380	460	—	—	55	50	80	80
15	140/85	130/80	750	600	90	85	50	50	130	140
16	125/60	125/60	610	650	110	115	70	70	140	150
17	130/80	105/70	760	665	125	115	70	70	170	170
18	130/70	140/80	665	600	110*	110*	—	—	130	130
19	140/90	120/80	600	640	95	100	85	85	150	160
20	100/70	58/0	835	835	90	100	85	80	140	140
Mean ±SD	132 ±27/78 ±11	113 ±26/67 ±11	754 ±158	740 ±171	99 ±26	95 ±27	66 ±29	65 ±27	128 ±30	134 ±29
	P<0 01		NS		NS		NS		P<0 01	

*A-to right bundle potential; His not obtained.

to henceforth are those determined by the chromatographic method.

EFFECTS ON SINUS RATE, ATRIOVENTRICULAR, AND INTRAVENTRICULAR CONDUCTION

There was no significant change in heart rate during or after quinidine infusion. Mean heart rate was 78±16 beats/min before quinidine and 79±18 beats/min at the time of peak plasma quinidine level. There was no significant difference between mean atrioventricular nodal conduction time before quinidine (99±26 ms) and a peak plasma quinidine level (95±27 ms). Two patients with prolonged control atrioventricular nodal conduction time (120 and 190 ms) showed slight decrease in AH time at peak plasma quinidine levels (to 115 and 180 ms, respectively).

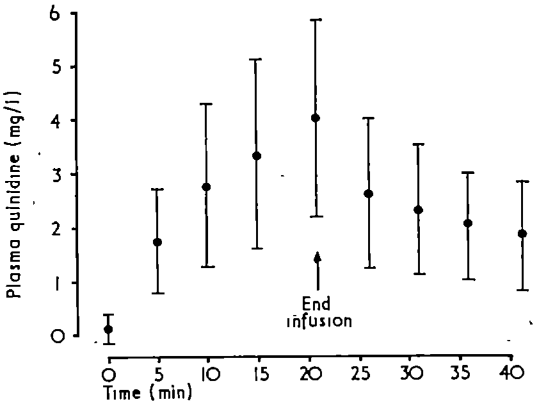

Fig. 1 *Mean (±SD) plasma quinidine level during and after infusion of quinidine gluconate. ↑ indicates time of termination of the infusion.*

The HQ interval was prolonged (>55 ms) in 10 of the 19 patients in whom it could be measured; the right bundle potential rather than the His potential was recorded in one patient. There was no significant difference between mean HQ before quinidine (66±29 ms) and at peak plasma quinidine level (65±27 ms). At peak plasma quinidine level, HQ was shorter in 4, longer in 7, and unchanged in 8 patients. In addition, there was no significant difference in absolute or per cent change in mean HQ before quinidine or at peak plasma quinidine level in the sub-group of 10 patients with prolonged control HQ compared with those with normal control HQ intervals. A His bundle electrocardiogram in a representative patient before quinidine infusion and at the time of peak plasma quinidine level is shown in Fig. 2. In one patient whose control tracing showed sinus bradycardia, left bundle-branch block, a split His potential, and a prolonged HQ interval, the sinus rate slowed even further and

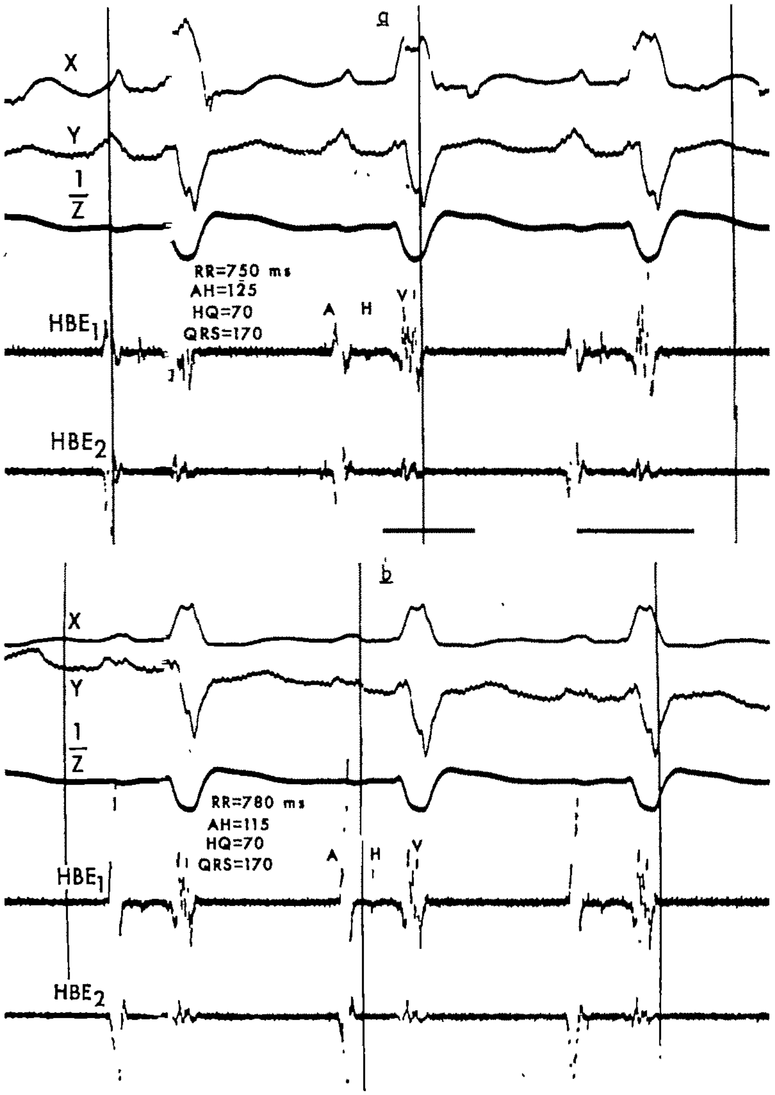

Fig. 2 *His bundle electrograms (HBE) of Case 17. (a) Before infusion of quinidine gluconate. A = atrial potential, H = His spike, V = ventricular potential. (b) HBE at peak plasma quinidine level. AH is 10 ms shorter than in (a) and HQ and QRS are unchanged.*

atrioventricular dissociation developed (Fig. 3), with the block localised within the His bundle during drug infusion. Second degree or complete atrioventricular block did not develop in any other patient.

Mean QRS duration increased significantly from 128±30 before quinidine to 134±29 ms at peak plasma quinidine level ($P < 0{\cdot}01$), but there was no significant difference in the absolute or per cent change in 7 patients with either normal or left anterior fascicular block compared with the 13 patients with bundle-branch block. In no patient did the QRS duration increase by greater than 28 per cent.

EFFECTS OF CONGESTIVE HEART FAILURE

Of the 20 patients, 13 were in congestive heart failure with varying degrees of compensation at the time of the study. The group in heart failure showed no significant difference from those not in heart failure, in heart rate or atrioventricular or intraventricular conduction times either before or after quinidine infusion. Furthermore, there was no difference in the peak plasma level of quinidine

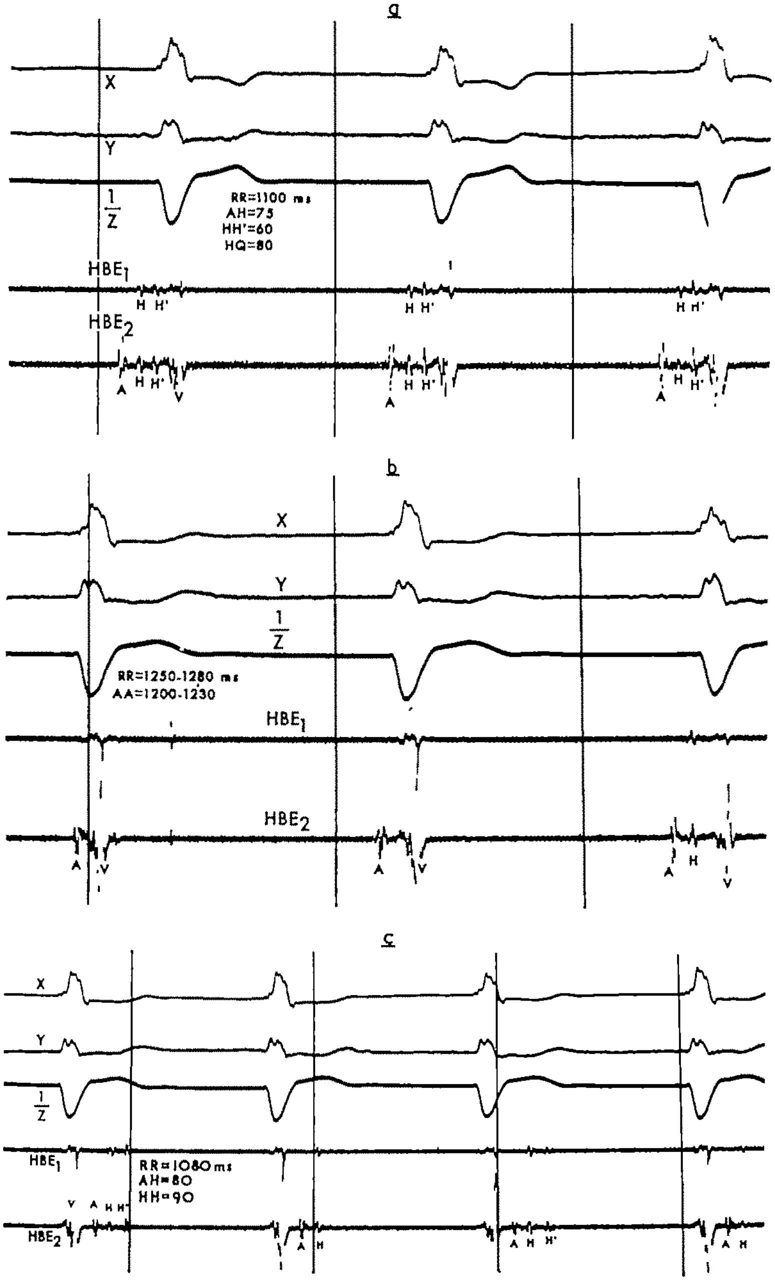

Fig. 3 *His bundle electrograms of Case 18. (a) Control tracing showing two spikes (HH') falling between A and V representing split His potential with spontaneous atrial cycle length of 1100 ms. (b) 5 minutes after termination of infusion, atrioventricular dissociation is present. (The atrial cycle length is 1230; the ventricular cycle length is 1280 ms.) Because of proximity of the atrial and ventricular electrogram, His spikes are not seen in the first two complexes. (c) Atrioventricular dissociation within the His-Purkinje system. Note that HH' has lengthened. H' is missing in alternate beats, which is probably because of block within the His. The ventricular pacemaker is probably in the distal His bundle, but a focus in the right fascicle cannot be excluded.*

achieved, when normalised for height and weight, in the patients in heart failure compared with the patients not in heart failure.

ARRHYTHMIA CONTROL

Five patients were having premature supraventricular beats and 8 were experiencing premature ventricular beats during the study. One of the subjects had both premature atrial contractions and premature ventricular contractions. Ectopic beats were decreased in frequency (< 75% of control) at the time of peak plasma quinidine level in all 9 patients in whom therapeutic levels were achieved. The effect on frequency of premature ventricular contractions in a representative patient is shown in Fig. 4.

TOXIC SIDE-EFFECTS

The mean of the systemic blood pressures dropped significantly ($P < 0.01$) from control values (132 ± 27/78 ± 11 mmHg) by 5 minutes after starting infusion and was lowest (113 ± 26/67 ± 11 mmHg) at the end of infusion when plasma quinidine levels were highest. Five patients had a drop in systolic blood pressure to < 100 mmHg but remained asymptomatic. In 2 other patients, diaphoresis and nausea occurred concomitantly with a distinct fall in blood pressure and small changes in heart rate; both responded favourably to raising the legs and stopping the infusion. Their plasma quinidine levels were not excessive (1·4 and 3·2 mg/l) at the time of hypotension and the rates of infusion (0·35 and 0·20 mg/kg per min) were no more rapid than in the remaining 18 patients (mean 0·34 mg/kg per min). No other toxic responses to quinidine infusion were observed, and no patients experienced tinnitus, vertigo, or diarrhoea.

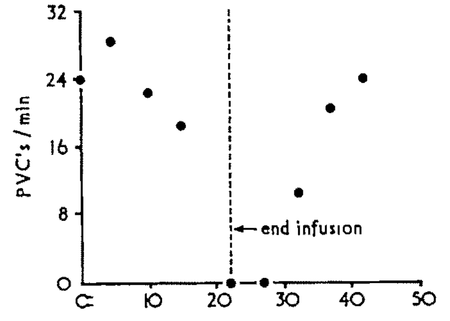

Fig. 4 *Frequency of premature ventricular contractions during quinidine infusion in Case 6 illustrating suppression of ectopic beats at termination of infusion and return of premature ventricular contractions afterwards.*

Discussion

EFFECT OF QUINIDINE

Quinidine is considered by many to be the mainstay of chronic oral antiarrhythmic therapy. It is of obvious practical importance for the clinician to be aware of the relative risks of quinidine therapy for patients with atrioventricular or intraventricular conduction delay. Experimental studies in animals showed that administration of quinidine in amounts that produce blood levels considered to be within the therapeutic range in man result in little change in atrioventricular nodal conduction time (Wallace *et al.*, 1966) but definite increases in infranodal and intraventricular conduction times (Wallace *et al.*, 1966; Sokolow, 1951; Vaughan Williams, 1958; Swain and Weidner, 1957). For this reason, some believe that the presence of bundle-branch block constitutes a relative contraindication to the use of quinidine (Sokolow and Perloff, 1961). The electrocardiograms in 16 of our patients had either unifascicular or bifascicular block and 10 had prolonged infranodal conduction times. Therapeutic blood levels of quinidine resulted in no significant change in atrioventricular conduction times and in small increases in intraventricular conduction times. Though the QRS duration increased significantly ($P < 0.01$) after quinidine, the QRS axis did not change nor did a new bundle-branch block develop in any patient. In one patient with sinus bradycardia and a prolonged sinus node recovery time, sinus slowing, and atrioventricular dissociation associated with an escape His bundle or fascicular focus developed during quinidine infusion. The degree of atrioventricular block did not increase in any other patient.

The only other study in which His bundle recordings were used to assess the effects of quinidine gluconate in man is that of Josephson *et al.* (1974), in which the drug was administered intramuscularly. Their results are similar to ours with regard to the effect of quinidine on heart rate and atrioventricular nodal and intraventricular conduction times but differ in that a small but significant increase in infranodal conduction time (mean 6 ms) was observed in their study. The reason for the difference is uncertain, though in the study of Josephson *et al.* (1974), larger doses (600 to 800 mg quinidine gluconate) were administered and His bundle recordings were made at higher plasma quinidine levels (4·6 versus 3·8 mg/l). It is also possible that the hypotension caused by intravenous administration of the drug in our patients provoked catecholamine stimulation or increased sympathetic tone which tended to diminish the direct effect of quinidine on the infranodal conduction system.

Reports on the safety of intravenous administration of quinidine have yielded conflicting conclusions. Severe toxic reactions (Chapman, 1945; Hepburn and Rykert, 1937; Riseman and Linenthal, 1941; Strong and Munroe, 1940) and death (Armbrust and Levine, 1950; Acierno and Gubner, 1951) were attributed to the intravenous route and some clinicians have expressed the view that the intravenous route is never (Selzer, 1972) or almost never (Goldberg, 1974; Friedberg, 1966) acceptable medical practice. In these reports either large doses of quinidine were administered (intravenously) rapidly or the patients appeared to be moribund at the time of infusion. However, Clagett (1950) administered quinidine lactate intravenously in doses up to 3·25 g but at infusion rates comparable to ours, and the only side-effects observed were nausea and vomiting in 3 of the 13 patients studied. In his study, as in ours, quinidine administration was associated with a decrease or abolition of supraventricular or ventricular arrhythmias and did not produce bundle-branch or atrioventricular block or increased ventricular ectopia. Asymptomatic mild to moderate decreases in systemic blood pressure occurred in 17 of our patients, including reduction of systolic pressure to < 100 mmHg in 5, and a toxic reaction characterised by the abrupt onset of nausea, intense diaphoresis, and severe hypotension occurred in 2 patients during infusion. Both of these patients actually received smaller amounts of quinidine because infusion was terminated prematurely, and plasma quinidine levels were in the subtherapeutic or low therapeutic range (1·4 and 3·2 mg/l). In all patients who had a fall in blood pressure, the hypotension persisted for 5 to 10 minutes after termination of infusion. Our data suggest that careful monitoring of the systemic blood pressure is mandatory when quinidine is administered intravenously. Moreover, an alpha-sympathetic agonist should be readily available because the hypotensive effect of intravenous quinidine is most likely the result of reversible alpha-receptor blockade (Ferrer *et al.*, 1948; Luchi *et al.*, 1963) rather than of a direct myocardial action.

PLASMA QUINIDINE LEVELS

Although there was a progressive rise in plasma quinidine level in each patient during infusion of quinidine, the levels ranged widely even after correction for rates of infusion and body weight. This finding is probably related to the rate and extent of drug distribution because only trivial amounts of the drug would be expected to be metabolised or excreted over the relatively short period of the study. Regardless of differences in rate and extent of drug distribution, we found that doses of 7 to 9 mg/kg quinidine gluconate regularly resulted in peak plasma quinidine levels within the therapeutic range. Of further interest was the observation that mean peak plasma quinidine levels did not differ significantly between patients with (10) or without (10) heart failure. These findings are similar to those described by Bellet *et al.* (1971), who found no significant difference in mean plasma quinidine levels between normal subjects and patients with congestive heart failure 2 hours after an oral dose of 600 mg quinidine; however, the levels were significantly higher in patients with heart failure than in normal subjects 4, 6, and 24 hours after the oral dose. These findings are consistent with our own unpublished observations that the higher plasma quinidine levels found in patients with heart failure are related to decreased drug clearance rather than to diminished volume of distribution.

CLINICAL IMPLICATIONS

In this study, the haemodynamic and electrophysiological effects of intravenous administration of quinidine gluconate which resulted in a relatively rapid achievement of therapeutic plasma quinidine levels were assessed. All the patients but one who received 7 to 9 mg/kg achieved therapeutic plasma quinidine levels within 22 minutes. In a recent study by Wellens and Durrer (1974) 4 mg/kg of quinidine was infused intravenously at a rate of 0·8 mg/kg per min in patients with the Wolff-Parkinson-White syndrome and 5 of the 6 patients became hypotensive, with sweating, restlessness, and tachycardia. In our study, the average total dose was about twice as great, but the slower rates of infusion (mean rate of 0·34 mg/kg) probably accounted for the lower incidence of toxicity. Nevertheless, the slower rates of infusion used in the present study were still associated with an unacceptably high incidence of hypotensive reactions. This study has also shown that therapeutic levels of quinidine were effective in decreasing or abolishing cardiac arrhythmias and were safe for patients with atrioventricular or intraventricular conduction abnormalities in that no higher degrees of atrioventricular block or increased ventricular ectopic activity were encountered. One patient with sinus bradycardia, however, developed transient atrioventricular dissociation owing to further slowing of the sinus rate. For patients requiring parenteral quinidine therapy, intravenous administration appears to have several advantages over the intramuscular route: there is a more rapid and uniform achievement of therapeutic plasma levels; drug administration may be readily terminated should untoward effects occur; and the intravenous route is painless.

Nevertheless, the relatively high incidence of hypotensive reactions encountered suggests that intravenous quinidine administration should be reserved for critical situations where first line drugs are ineffective and only used with ready availability of an alpha-sympathetic agonist. Though untoward effects disappeared shortly after termination of the infusion and no long-term sequelae were observed, this regimen should rarely, if ever, be used in critically ill patients with hypoxia and/or electrolyte abnormalities (Watanabe *et al.*, 1963; Watanabe and Dreifus, 1967; Holland, 1957), in patients with sinus bradycardia, or in patients receiving drugs that may potentiate quinidine effects.

Addendum

Since completion of this manuscript, 7 additional patients received 8 mg/kg of quinidine intravenously and no untoward effects were observed.

The authors wish to thank Gunnard Modin for statistical analyses.

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Effect of positive acceleration (+gz) on electrocardiogram of subjects with vasoregulatory abnormality

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ST-T wave changes in the electrocardiogram detected during routine examination and aggravated by erect posture, hyperventilation, and exercise in apparently healthy young individuals have been termed vasoregulatory abnormalities. No evidence of ischaemic heart disease has been found in such subjects.

Ten young healthy air crew with vasoregulatory abnormalities were subjected to maximal exercise on treadmill and procedure repeated after 120 mg propranolol daily for 3 days. After one week, they were subjected to a stress of positive acceleration (+gz) in a human centrifuge at 2·5 g *and 3·5* g *for 15 seconds each at a constant rate of rise of 0·1 g/s and the electrocardiogram was monitored during and in the post-acceleration phase. The procedure was repeated after propranolol 120 mg daily for 3 days. The stress of positive acceleration resulted in pronounced prominence of P waves and inversion of T waves (as has been reported in normal subjects) with minimal ST depression in the electrocardiogram. ST segment depression during exercise, at heart rates corresponding to those achieved during peak centrifuge runs, was significantly more pronounced. The ST, P, and T wave changes were returned to normal after propranolol.*

It is concluded that minimal ST segment depression after stress of positive acceleration as compared with conspicuous ST segment depression during exercise at corresponding heart rates, and their normalisation after propranolol, rules out ischaemia as an aetiological factor in subjects with vasoregulatory abnormalities.

It is not uncommon to find 'false positive' electrocardiographic ischaemic responses to exercise in certain subjects (Guzman and De la Cruz, 1972). Similar changes have been reported when the upright posture has been assumed and on hyperventilation (Kemp and Ellestad, 1968; McHenry *et al.*, 1970; Biberman *et al.*, 1971). They were attributed to autonomic influences (Nordenfelt, 1941) and labelled vasoregulatory abnormalities by Friesinger *et al.* (1972). When encountered among asymptomatic healthy individuals, the responsibility of the physician to give a definite diagnosis, especially to air crew, is tremendous. No evidence of ischaemic heart disease has been found in such subjects (Friesinger *et al.*, 1972). It was, therefore, decided to study the effect of the stress of positive acceleration forces and the resulting alterations in cardiovascular haemodynamics on the electrocardiogram of such subjects. This stress, in which the inertial vectors resulting from acceleration are directed parallel to the cardiovascular axis, has been termed positive *g* or +*gz*. Though cardiovascular reaction and electrocardiographic changes resulting from these accelerations in normal subjects have been reported earlier (Cohen and Brown, 1969a), the effect of +*gz* acceleration on the electrocardiogram of subjects with vasoregulatory abnormalities has not been reported hitherto, and now forms the basis of this study.

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Subjects and methods

Fifty-eight subjects out of a total 800 cases referred to this laboratory for cardiovascular evaluation were found to have vasoregulatory abnormalities as defined by Friesinger *et al.* (1972).

Of these 58, 10 were healthy male air crew, aged 22 to 36 years (mean 30 years), who volunteered to undergo further testing in a human centrifuge. All were found to have an abnormal resting or exercise electrocardiogram during routine medical check-up. They were evaluated clinically and biochemically. An electrocardiogram was recorded at rest and after a double Master's two-step exercise test. All of them showed ST-T changes in inferior leads, with or without involvement of lateral chest leads. They were then subjected to a multistage treadmill stress test. The details of the procedure for the treadmill stress test followed in this laboratory have been reported earlier (Balasubramanian *et al.*, 1975).

The electrocardiogram which monitors chest lead V5 was recorded in the supine and standing positions, after the Valsalva manoeuvre and hyperventilation, respectively. This was followed by maximal exercise on an Avionics motor driven treadmill by multistage stress as recommended by Bruce and Hornsten (1969). Heart rate and ST segment depression were monitored by an on-line digital Avionics computer model 2900. The test was repeated after propranolol 120 mg daily (40 mg × 8 hourly) for 3 days within 60 minutes of the last dose of the drug.

All the subjects were then familiarised with the environment of acceleration in the human centrifuge and were studied after a week of stopping propranolol. The centrifuge has its gondola mounted at a radius of 500 cm from the centre of rotation with the seat inclination 15° beyond 90°. They were then instrumented for electrocardiographic recording from the centrifuge, using a special floating type of electrode which does not come directly in contact with the skin. The contact is established through the conducting jelly. The leads were used as the input for triple electrocardiogram amplifiers model E-33 and recorded on a 6-channel jet recorder (Mingograph). The amplifier system permits selective switching of inputs. To ensure uniformity leads II, aVF$_z$ and V5 were recorded in all cases. After instrumentation of the subjects, the electrode connections were tested to ensure impedance values of less than 5000 ohms at the skin to electrode interface with a maximum difference of 1000 ohms between electrodes.

After obtaining a baseline record, the subjects were exposed to the following centrifuge profiles: (a) peak 2·5 *g* and 3·5 *g* for 15 seconds each; (b) constant rate of rise 0·5 *g*/s; (c) rate of decay 0·1 *g*/s; and (d) monitoring was continued during the acceleration period and for 3 minutes thereafter. Each subject was observed through a television screen during the entire procedure.

Loss of peripheral vision (greyout), if any, was recorded by the subjective response of the individual to a fixed set of peripheral lights. The procedure was repeated after propranolol 120 mg (40 mg × 8 hourly) daily for 3 days. The graphs were analysed and the heart rate was determined from successive RR intervals. Changes in P, QRS, T, and ST segment contour were recorded.

Results

Twenty treadmill stress tests and 20 centrifuge runs were completed on the 10 subjects. The response of heart rate and ST segment, as obtained from lead V5, to various manoeuvres and stresses is summarised in Table 1. Fig. 1 shows the ST response to various manoeuvres and exercise before and after propranolol. Minimal ST depression, frank inversion of T waves, and prominence of P waves were noted during the centrifuge run. Fig. 2 shows the ST response, and the contour changes in P and T waves during +*gz* acceleration before and after propranolol. ST segment changes during +*gz* stress before propranolol were insignificant and, like P and T wave changes, were completely normalised by propranolol. No intraventricular conduction disturbance or changes in rhythm were noted during any of the centrifuge runs. ST segment response to +*gz* acceleration was significantly less pronounced ($P < 0{\cdot}001$) as compared with ST segment response during exercise at corresponding heart rates. None of the subjects complained of fainting or manifested greyout at the *gz* profiles used.

Table 1 *Heart rate and ST segment response in 10 subjects with vasoregulatory abnormality*

		Supine	*Standing*	*Valsalva*	*Hyperventilation*	*Maximal exercise*	*gz acceleration*	
							2·5 g	*3·5 g*
Heart rate/min	B	85 (68–92)	107 (82–120)	118 (92–144)	131 (82–173)	185 (149–202)	123 (110–140)	125 (100–155)
	A	60 (54–73)	72 (60–87)	69 (54–85)	82 (64–104)	130 (102–159)	68 (60–83)	76 (60–100)
ST segment (mV)	B	−0·7 (+0·0 to −1·2)	−1·3 (−0·2 to −2·0)	−2·0 (−0·9 to −3·9)	−2·6 (−0·9 to −4·2)	−4·0 (−0·2 to −7·1)	−0·8 (−0·3 to −1·0)	−1·0 (−0·5 to −1·5)
	A	0·2 (+0·8 to −0·7)	0·2 (+0·8 to −0·7)	0·5 (+0·8 to −1·0)	0·1 (+0·8 to −1·2)	−1·4 (−0·3 to −1·5)	0·2 (+0·0 to 0·8)	0·3 (+0·1 to 0·6)

B, before propranolol; A, after propranolol; mV, millivolts; −, below isoelectric level; +, above isoelectric level.
Figures in parentheses represent range.

Discussion

The 10 subjects reported in this study form a small subset of cases who are found to have an abnormal electrocardiogram, particularly on assuming an upright posture, after hyperventilation and the Valsalva manoeuvre. The electrocardiographic changes are usually confined to leads II, III, aVF, and V4 to V6. In the majority of our cases the changes were initially aggravated by exercise but disappeared or improved as the exercise proceeded. They did not manifest any symptoms even at the height of maximal exercise. Unlike the findings of Friesinger *et al.* (1972), the ST-T changes were also

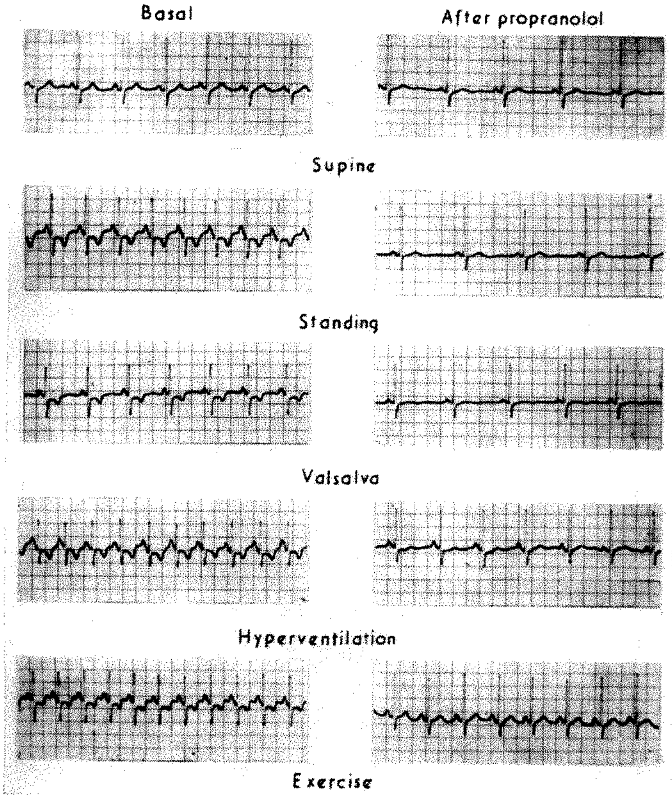

Fig. 1 *Electrocardiogram of a subject with vasoregulatory abnomalities in the supine position, on standing, during hyperventilation, Valsalva manoeuvre, and exercise. Panel on the left shows electrocardiograms before the drug and the one on the right, after propranolol.*

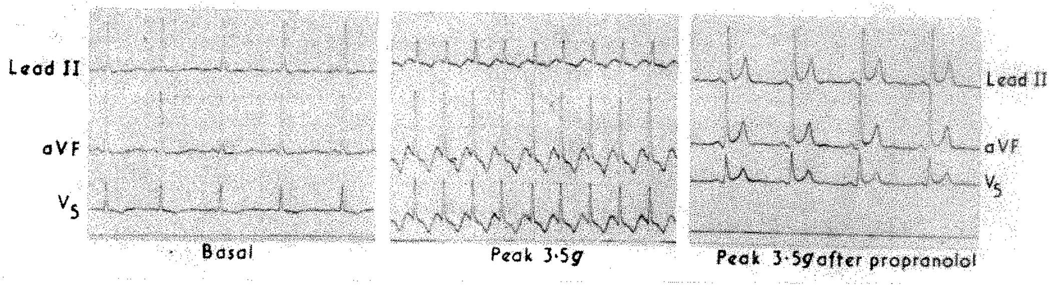

Fig. 2 *Electrocardiogram of a subject with vasoregulatory abnormalities recorded before centrifuge run—basal (left panel), during centrifuge run at 3·5* g *peak, without propranolol (central panel), and after propranolol (right panel).*

aggravated by the Valsalva manoeuvre. Therefore, the changes attributed to increased sympathetic tone (Nordenfelt, 1941) may essentially be the result of an unstable autonomic nervous control (Holmgren *et al.,* 1959; Levander-Lindgren, 1964). It has not been possible to rule out categorically an ischaemic aetiology in these cases, but the clinical picture, electrocardiographic changes, normalisation of these under beta-blockade, and normal coronary arteriograms in some of them have been used as evidence against ischaemia (Friesinger *et al.,* 1972). Positive acceleration in normal individuals results in progressive flattening of the T wave going on to frank T inversion and distinct peaking of the P waves. These changes are confined to leads II, III, aVF, and V4 to V6. A distinct increase in the amplitude of the P waves was found in 78 per cent of 18 subjects exposed to 116 centrifuge runs (Cohen and Brown, 1969b) and 100 per cent of 20 subjects exposed to 40 centrifuge runs (Rai and Dham, 1973). T wave changes were, however, noted in 100 per cent and 80 per cent of the subjects in the two series, respectively. Our findings in subjects with vasoregulatory abnormalities are similar to those found in normal subjects by these workers. Electrocardiographic changes during positive acceleration in normal subjects have been attributed to myocardial ischaemia (Gauer, 1950; Gauer and Zuidema, 1961; Zuidema *et al.,* 1956), to descent of the diaphragm (Browne, 1958–1959), and related to heart rate (Bjurstedt *et al.,* 1959). Nordenfelt (1961) was, however, unable to reverse these changes produced by orthostasis with rate slowing carotid massage. Similar P and T wave changes have been produced by administration of sympathomimetic drugs and abolished by beta-blockers (Sjöstrand, 1950).

Positive acceleration results in pronounced haemodynamic alterations which have been reported earlier (Gauer, 1950; Gauer and Gienapp, 1950; Zuidema *et al.,* 1956; Gauer and Zuidema, 1961; Wood *et al.,* 1961). These consist of a fall of venous return to the heart, a decrease in left ventricular end-diastolic pressure, a diminution in the aortic root pressure and left ventricular dp/dt. There is a rise in heart rate, though bradycardia has also been reported (Peterson *et al.,* 1975). Calculated peripheral resistance begins to increase very early and remains high at the peak of *gz* acceleration. It is directly proportional to the level of *gz* acceleration. Most of these values have a tendency to overshoot before return to control levels in the post acceleration phase. Though coronary flow has not been estimated in humans during acceleration, animal experiments have shown that coronary flow increases at low *g* forces but decreases at higher *g* forces (Shubrooks *et al.,* 1975). These workers have shown an increase in coronary flow and a decrease in coronary resistance in experimental animals subjected to positive acceleration, in spite of a fall in coronary perfusion pressure.

Our data have shown that electrocardiographic changes during positive *gz* acceleration in cases with vasoregulatory abnormality are not essentially different from normals. The P and T waves behave exactly as they do in normal subjects. The ST segment depression which is much more distinct after assumption of the upright posture, hyperventilation, and Valsalva manoeuvre, is much less so during the centrifuge run, and like P and T wave changes is completely normal with beta-blockade.

In addition to haemodynamic alterations produced by acceleration in the +*gz* axis, positive acceleration produces a reduction in the arterial pressure at head level. This in turn results in tachycardia and reflex vasoconstriction (Cohen and Brown, 1969a). Similar changes take place after orthostasis, and the similarity between the findings seen during positive acceleration and orthostasis is worth noting. Since the changes in both situations are normalised by beta-blockade, sympathetic stimulation is probably the common denominator in both the situations (Cohen and Brown, 1969a; Nordenfelt, 1965). Minimal ST deviations seen in our cases during positive acceleration and their normalisation with beta-blockade compared with much more pronounced changes during Valsalva and hyperventilation rules out the possibility of an ischaemic aetiology. The ST segment response is not rate related, because at a similar heart rate after exercise and +*gz* acceleration, the ST response is significantly different (Table 2). It may be argued that significantly less ST depression secondary to

Table 2 *Maximal ST segment and heart rate response to +gz at 3·5 for 15 sec and ST segment response to treadmill exercise at corresponding heart rates in subjects with vasoregulatory abnormality*

Case No.	*HR/min*	*ST gz*	*STE*
1	136	−0·9	−2·6
2	100	−0·5	−1·9
3	125	−1·1	−2·3
4	100	−0·8	−2·0
5	155	−1·0	−4·2
6	125	−1·4	−2·7
7	115	−0·6	−2·0
8	130	−0·8	−2·4
9	132	−1·4	−3·8
10	132	−1·85	−2·6

ST *gz*, ST segment response to 3·5 *g*; STE, ST segment response to exercise; −, below isoelectric level.

$+gz$ acceleration is the result of improvement in coronary flow and fall in coronary resistance as seen in experimental animals (Shubrooks *et al.*, 1975). Beta-blockade, however, results in an increase in coronary vascular resistance (Jorgensen *et al.*, 1973) and would, therefore, result in aggravation of these changes. It seems highly likely that beta-blockade in combination with $+gz$ acceleration would result in an increased incidence of fainting reactions but we were surprised to find that none of the subjects had any such reaction or decrease in tolerance to $+gz$ in the form of greyouts. Cohen and Brown (1969a) exposed their subjects to progressively increasing acceleration profiles and greyouts were noted only beyond $+4g$. Administration of propranolol did not significantly affect the tolerance to $+gz$, though 3 out of 10 subjects stated that their greyouts seemed to progress more rapidly after propranolol administration. We did not expose our subjects to more than $+3{\cdot}5g$ and that may explain the absence of greyouts. As stated above, positive acceleration produces a reduction in the arterial pressure at head level and when combined with beta-blockade, a further fall in systemic arterial pressure may aggravate this. Beta-blockade is also known to increase the alpha-adrenergic activity of the venous capacitance vessels and may thus indirectly induce venoconstriction (Harris *et al.*, 1966). Propranolol, by increasing the diastolic filling time secondary to slowing of the heart, may neutralise the effect of the peripheral venous pooling effects of $+gz$ acceleration. Propranolol also causes significant myocardial depression in man (Sjöstrand, 1950; Lucchesi, 1965; Paley *et al.*, 1965). It is, therefore, possible that the sum total of various haemodynamic alterations caused by $+gz$ acceleration may be neutralised by propranolol. The fact that the ST changes are significantly less at a similar heart rate during $+gz$ acceleration than during various manoeuvres and exercise, is evidence against ischaemia, as the basic aetiology in these cases with grossly abnormal ST segment. This supports the hypothesis put forward by Nordenfelt (1941) and Friesinger *et al.* (1972) that ST-T changes in such subjects are not caused by ischaemia and subjects with these abnormalities can undergo severe physical stress including flying aircraft involving $+gz$ acceleration. Subjecting these asymptomatic individuals to invasive procedures of coronary arteriography may not be justified, but follow-up of these subjects is needed in order to find an answer to this question.

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Case reports

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Right-sided endocarditis involving both tricuspid and pulmonary valves in a patient with ventricular septal defect

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A patient with alpha-haemolytic streptococcus endocarditis on a ventricular septal defect is described. The disease spread to involve both tricuspid and pulmonary valves which were largely destroyed. The patient developed severe right heart failure with pronounced rise in right atrial pressure. This led to right-to-left shunting through the foramen ovale with systemic embolization. She was successfully treated by operative closure of the defects and double right-sided valve replacement.

The pathology and clinical features of right-sided endocarditis are very different from its left-sided counterpart. In addition to posing problems of diagnosis and treatment, pure right-sided endocarditis may give rise to unfamiliar and interesting haemodynamic situations. The following case illustrates these points.

Case history

A married woman, now aged 27 years, presented to the Department of Cardiology in September 1974 during her second pregnancy. She was known to have had a murmur from childhood but was asymptomatic. Physical examination showed a healthy woman with a harsh pansystolic murmur maximal at the left sternal edge. A clinical diagnosis of a small ventricular septal defect was made and in February 1975 she underwent full-term normal delivery under antibiotic cover.

Four months later she was admitted as an emergency. For two weeks she had suffered progressive weakness, malaise, diarrhoea, cough, abdominal swelling, ankle oedema, and shortness of breath. There was no history of recent dental treatment. On examination she was pale, febrile, and extremely unwell. Her pulse was regular at 110/min. The jugular venous pressure was raised 5 cm above the sternal angle with prominent *v* waves. The ventricular impulse was diffusely increased and there was a systolic thrill. The pansystolic murmur was unchanged. A prominent early diastolic murmur was heard at the left sternal edge. This was decrescendo in nature and did not vary with respiration. She was tachypnoeic and there were bilateral basal crepitations. Finger clubbing was not noted. Ascites was detected in the abdomen and a grossly enlarged, tense, non-pulsatile liver extended below the umbilicus. Examination of the central nervous system was normal apart from a long-standing divergent squint. Six blood cultures were taken and the patient was started on penicillin 20 megaunits daily and streptomycin 500 mg daily, with digitalis and diuretics.

Initial investigations showed her to have a microangiopathic haemolytic anaemia. (Haemoglobin 6·0 g/100 ml, platelets 70 000/mm^3, reticulocytes 7 per cent. Fibrinogen 80 mg/100 ml fibrin degradation products 40 μg/ml. Erythrocyte sedimentation rate 136 mm/hr. Blood urea 25·1 mmol/l.) Intravenous mannitol was added to her treatment because the deterioration in renal function was thought to be the result of coagulation in small vessels. Serum complement was persistently low with increased urinary red cell excretion. Five of the blood cultures grew *Streptococcus mitior* (an alpha-haemolytic oral commensal). The organism was fully sensitive to penicillin and the streptomycin was stopped. Adequate blood levels of penicillin were achieved for 6 weeks. On this regimen the patient improved and her renal function and blood picture returned to normal. Six carious teeth were initially extracted and subsequently a full dental clearance was undertaken. Five days after admission she developed pleuritic chest pain, right calf tenderness, and patchy shadowing in the right lower zone on the chest *x*-ray film. She was treated with heparin. For the next two months she suffered from recurrent chest problems involving mainly the right base.

One month after admission she was still very ill. In view of persisting anaemia and gross hepatomegaly a liver biopsy was performed which showed the changes of chronic venous congestion only. She also had a renal biopsy in view of a chronically raised erythrocyte sedimentation rate and very low serum complement levels. The appearances were compatible with a healing nephritis associated with infective endocarditis.

Three months after admission she was noted to have central cyanosis and finger clubbing. She developed sudden blindness in the right eye caused by a retinal embolus. Her general condition was deteriorating and frusemide, 120 mg daily, was not controlling her fatigue and dyspnoea.

Cardiac catheterization showed a very large right atrium. A right atriogram, though inconclusive, strongly suggested a right-to-left shunt at atrial level. The shunt across the ventricular septal defect was less than 2:1. The ventricular septal defect was crossed. Aortic O_2 saturation was 64 per cent. No aortic regurgitation was seen on aortography. Pressures (mmHg): right atrium a=10, v=15; right ventricle 35/5; pulmonary artery 34/5. Left ventricular end-diastolic pressure 8. The Figure shows the pressure withdrawal trace from the pulmonary artery to the right atrium.

The clinical picture and catheter data were interpreted as showing severe pulmonary and tricuspid regurgitation with no evidence of left-sided valve dysfunction. The ventricular septal defect was considered haemodynamically insignificant. A patent foramen ovale was probable. She was referred for operation.

Operation: 13 November 1975. One-hour circulatory occlusion with deep hypothermia. Operative findings were a patent foramen ovale and a ventricular septal defect measuring 5 mm × 5 mm in the membranous septum. Both tricuspid and pulmonary valves were largely destroyed and a large defect in the septal cusp of the tricuspid valve was noted. There were lumps of yellowish material hanging from some cusps and strands of this extended 4 cm into the pulmonary artery. (The valves were sterile on culture. Histology showed some fibrosis with fibrinous thrombus on the valve surfaces. The vegetations contained numerous gram positive cocci.)

Procedure: The defects were closed with sutures. Both valves were totally excised and replaced by Lillehei Kaster prostheses. Postoperatively the patient made a good recovery. She is no longer cyanosed and the jugular venous pressure is normal. The liver is no longer palpable. Her diuretics have been stopped.

Discussion

Right-sided endocarditis is rare in the absence of predisposing factors. The most common of these are chronic heroin addiction and congenital heart disease (Roberts and Buchbinder, 1972). The organism is frequently a staphylococcus and the clinical course is dominated by septic pulmonary infarction and septicaemia. Right heart failure, cardiac murmurs, clubbing, and systemic emboli are seldom prominent though evidence of nephritis is frequent (Bain *et al.*, 1958). The tricuspid valve is usually involved though occasionally the pulmonary valve is affected as well, or in isolation.

It is well known that isolated tricuspid regurgitation can be tolerated very well if there is no pulmonary hypertension. Patients with traumatic tricuspid regurgitation have survived for many years (Marvin, Schrank, and Nolan, 1973) and total

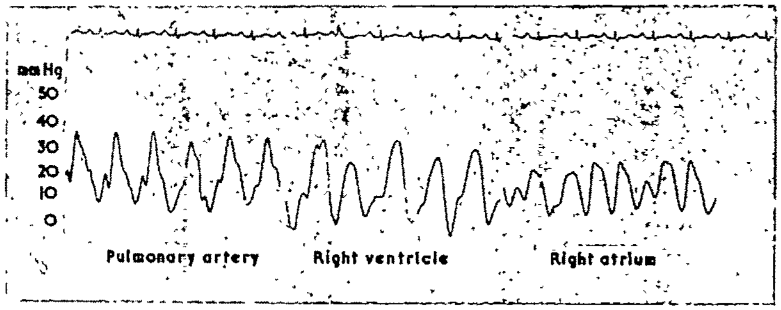

Fig. *Pressure withdrawal trace from pulmonary artery through the right ventricle to the right atrium showing the wide pulse pressure in the pulmonary artery and the large systolic waves in the right atrium.*

removal of the tricuspid valve without replacement has been recommended as a life-saving measure in endocarditis associated with heroin addiction (Arbulu, Thoms, and Wilson, 1972). A recent survey, however, showed that 3 patients out of 10 who had this procedure developed right heart failure and it was not possible to identify those at risk from preoperative data (Robin *et al.*, 1975).

Isolated pulmonary regurgitation may also be tolerated well and is compatible with many years of freedom from symptoms (Holmes, Fowler, and Kaplan, 1968; Olesen and Fabricius, 1956). Experiments in dogs support this though the survival of dogs with excised pulmonary valves is very much reduced if there is an associated ventricular septal defect or right ventriculotomy (Ellison *et al.*, 1970). It seems, therefore, that regurgitation or complete absence of either right-sided valve can be well tolerated, but under such circumstances the ventricle is handicapped and little able to cope with further insults. In our case double valve disease constituted such an insult.

The late development of clubbing in our patient was of interest since it coincided with the onset of central cyanosis. The absence of fever, negative blood cultures, and falling erythrocyte sedimentation rate at this time suggested that the clubbing was more likely to be the result of the development of cyanotic heart disease than of persisting infection.

Sporadic reports of right-sided endocarditis on both valves, with a ventricular septal defect, occur in post-mortem series (Boldero and Bedford, 1924). Some haemodynamic data are available on mixed right-sided endocarditis in heroin addicts. Massumi, Just, and Tawakkol (1967) report two such cases, one of whom was living after two years with apparently severe regurgitation of both valves. Surgical intervention has been described in isolated tricuspid endocarditis with a ventricular septal defect (Jimenez-Martinez, Lopez-Cuellar, and Quioñones-Morales, 1971). To our knowledge there has been no report of a ventricular septal defect with right-sided endocarditis on both valves treated by total surgical correction. In studies of necropsy material it was shown that right-sided endocarditis seldom spreads to involve the valve ring and the authors concluded that good results could be expected from operation (Roberts and Buchbinder, 1972). Our case is certainly in accord with this conclusion.

We thank Dr. C. H. J. Swan who originally referred the case and subsequently performed the liver biopsy. We are also indebted to Dr. G. M. Aber and Dr. P. Naish who helped with the management of the renal complications and performed the renal biopsy.

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Pulmonary embolisation of retained transvenous pacemaker electrode

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When removal of an endocardial pacemaker electrode became necessary in a patient with congestive myocardiopathy, it proved to be incarcerated. Therefore, a portion of it had to be left in site after cutting the external end of the pacing catheter. During follow-up examinations the electrode was seen to migrate in the large veins and finally was found embolized into a pulmonary artery. While there have been publications on the migration of retained pacemaker electrodes before, to our knowledge this represents the first case reported with pulmonary embolization of the migrating fragment.

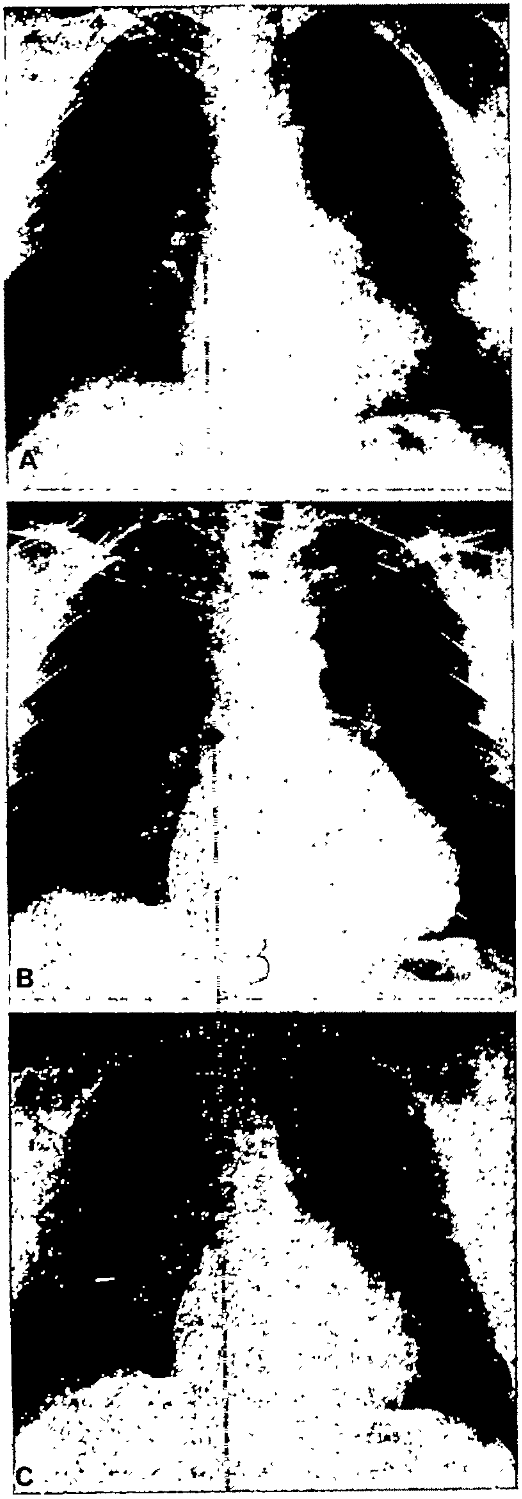
Migration of a retained pacemaker electrode is an extremely rare event which has been reported only four times (Ramo *et al.*, 1968; Tallury *et al.*, 1972; Das *et al.*, 1974; Soni, Lupi, and Mispireta, 1974). The following case differs from those described previously in that the migrating electrode left the venous system and was embolized into a major pulmonary artery. While pulmonary emboli originating from thrombi surrounding a transvenous pacemaker electrode do occasionally occur (Prozan *et al.*, 1968; Marx *et al.*, 1972), the patient described in this paper represents, to our knowledge, the first case of pulmonary embolization of the electrode itself.

Case report

The patient suffering from familial congestive myocardiopathy was first seen at our hospital in 1961 when he was 27 years old. During the following years he had to be admitted to hospital repeatedly for congestive heart failure. On all these occasions his electrocardiogram revealed atrial fibrillation with a slow ventricular response, and over the years there was a tendency to a progressive decrease in ventricular rate which had dropped to 30 beats/min by July 1973. It was then decided to implant a permanent R-wave-inhibited demand pacemaker and the procedure was performed on 13 July 1973, using a unipolar pervenous electrode (Elema EMT 588 A) introduced via the right internal jugular vein.

Subsequently several complications were encountered. An infection with *Staphylococcus aureus* developed at the implantation site necessitating removal of the pulse generator three weeks after its implantation. Another three weeks later a new pacer was implanted subcutaneously at the left pectoral area and was connected to the original electrode which had been left in place. Since signs of infection were noted over this implantation site as well, and as it was felt that the obviously persisting infection could only be eradicated by explanting the entire pacing system, it was decided to remove the pulse generator and the electrode on 6 February 1974. During the operation the electrode could not be pulled back any further beyond the right innominate vein. Therefore, it was cut near the point of its entrance into the jugular vein, and after the proximal portion had been removed, the distal portion was anchored with several transfixation sutures to the platysma. During the following months, while the patient's rate was controlled by medical treatment alone, a fistula developed at the original operation site over the internal jugular vein which was excised on 27 December 1974. While searching for the electrode tip on this occasion the internal jugular vein was lacerated and because of severe bleeding no further attempt was made to locate and remove the electrode tip.

The patient was next seen on 21 January 1975, after an epileptic seizure secondary to a cerebral embolus. At that time the pacemaker electrode tip was still visible on a chest *x*-ray film at its original



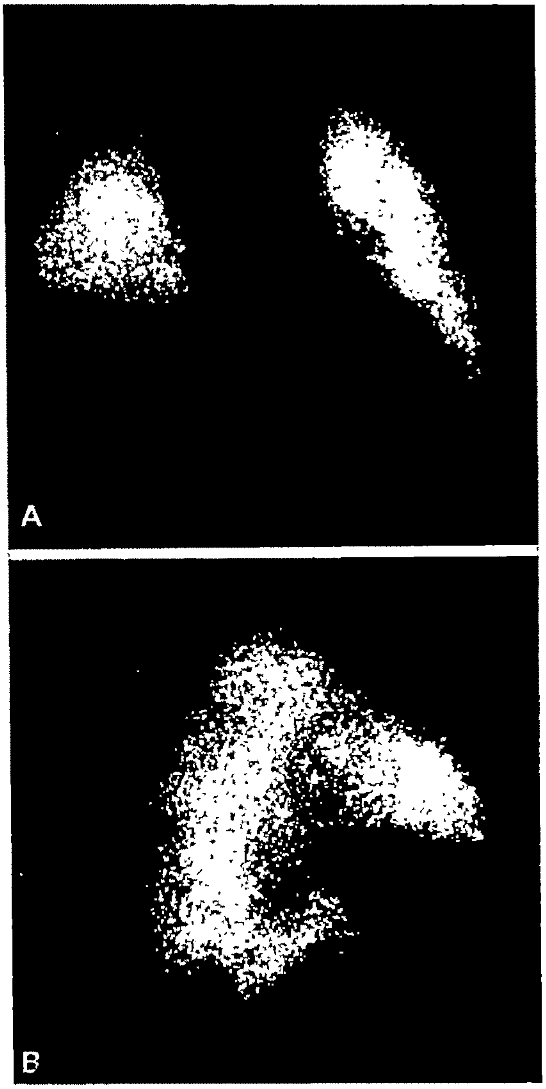


FIG. 2 *Lung scan revealing lack of perfusion of the entire middle lobe of the right lung. (A) antero-posterior view; (B) right view.*

FIG. 1 *Chest x-ray films showing the location of the ← severed proximal end of the pacemaker electrode: (A) 21 January 1975: right innominate vein; (B) 24 April 1975: superior vena cava; (C) 4 September 1975: pulmonary artery of the right middle lobe.*

position in the right innominate vein (Fig. 1A). On the next x-ray film during a routine visit on 24 April 1975, the tip of the electrode was located further down in the area of the superior vena cava (Fig. 1B), and when the patient was seen again on 4 September 1975, the electrode was found in the right middle lobe of the lung (Fig. 1C), and under fluoroscopy appeared to be lodged in the pulmonary artery of the right middle lobe. This was confirmed by lung scan which revealed lack of perfusion of the entire middle lobe of the right lung (Fig. 2). Physical examination of the lung, blood gas analysis, and pulmonary function tests were all within normal limits and no significant changes were found in the electrocardiogram as compared with that registered in April 1975. Careful questioning of the patient indicated no history suggestive of pulmonary embolisation or febrile disease during the months between April and September 1975.

Discussion

Electrode displacement and skin erosion with secondary infection are the complications which most commonly require replacement of an endocardial pacing electrode (Schmuck *et al.*, 1974). In cases of electrode displacement it is considered safe to leave the old electrode in place if it cannot easily be removed. In contrast, it is considered mandatory to remove pacing wires in cases of infection in order to control local and systemic septic complications (Imparato and Kim, 1972a). Special techniques have been described for the removal of these electrodes in cases where simple retraction proves impossible, because the electrode has become 'trapped' in the endocardium of the right ventricle (Imparato and Kim, 1972b). In other instances, the pacing electrode can successfully be dislodged from the right ventricle, but cannot be removed entirely from the venous system because fibrous bands—surrounding the pacing wire at portions where it had become attached to the ventricular musculature and the venous pathway—hinder its complete removal.

Suturing the stump of such electrodes to the surrounding tissues does not always successfully prevent secondary displacement as was observed on four occasions by different authors who reported migration of a retained endocardial pacemaker electrode (Ramo *et al.*, 1968; Tallury *et al.*, 1972; Das *et al.*, 1974; Soni *et al.*, 1974). In all of these 4 cases the pacing electrodes remained in the large veins and eventually drifted to the inferior vena cava and the iliac veins, from where they could be removed either with snare type catheters inserted via the saphenous vein or by laparotomy.

The migration of foreign bodies in the venous system is influenced by several factors, the most important ones being the velocity of blood flow, the body position, and specific gravity of the foreign body. It is, therefore, not surprising that most of the papers on dislodgement of indwelling polyethylene catheters (low specific gravity) report subsequent embolization 'down-stream' to the right atrium, right ventricle, or pulmonary artery, as described in the first publications (Turner and Sommers, 1954; Knutson and Stenberg, 1959). In contrast, foreign bodies which are totally or partially of metallic nature and hence have a high specific gravity appear to have a tendency to migrate under the influence of gravity—even 'up-stream'—towards the inferior vena cava and the iliac veins, as was shown in previous reports on electrode migration (Ramo *et al.*, 1968; Tallury *et al.*, 1972; Das *et al.*, 1974; Soni *et al.*, 1974) and on the displacement of the metallic tip of a coronary suction catheter during cardiac surgery with cardiopulmonary bypass (Irmer, 1964). In these latter cases the body position at the moment of migration must play the dominant role and this may also explain the peculiar embolization of the pacing electrode to a pulmonary artery in our patient.

Therapeutic recommendations concerning pulmonary embolization of foreign bodies in general include its removal by thoracotomy or by transvenous retrieval with snare type catheters (Irmer 1964; Bernhardt, Wegner, and Mendenhall, 1970; Dhingra, Rosen, and Rahimtolla, 1973). The main reasons for this aggressive management are reports of perforation (Brown and Kent, 1956; Johnson, 1966) and sepsis (Ayers, 1957; Wellmann, Reinhard, and Salazar, 1968) complicating cases of polyethylene catheter embolization. However, there have also been reports of successful conservative treatment of such cases (Borgeskov, Lauridsen, and Rygg, 1966; Bloos, Flörkemeier, and Schmücker, 1972).

In our case the event of embolization had evidently occurred without any symptoms noticeable by the patient. By the time it was diagnosed, no major disturbances of cardiac or pulmonary function could be discerned. By now the patient has been under observation for 5 months since the diagnosis of electrode embolism was first made, and control chest x-rays and lung scans have shown no further migration of the electrode. It can be assumed, therefore, that the pacing electrode has been wedged firmly in the pulmonary artery and has probably been surrounded tightly by thrombotic and fibrotic material. The risk of removing the pacemaker electrode is, therefore, considered to be greater than the risk of perforation. Besides, the possibility of sepsis originating from the electrode can be assumed to be very small in view of the previous good tolerance of the foreign body, which by now has been in the blood stream untouched for more than 15 months from the last operative procedure involving the implantation site.

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Wolff-Parkinson-White syndrome
Circus movement tachycardia dependent on procainamide

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A patient with Wolff-Parkinson-White syndrome was disabled by rapid ventricular rates during atrial arrhythmia and by periods of asystole. Circus tachycardia was induced by atrial stimulation only after the administration of procainamide. Nevertheless, treatment with this drug controlled the ventricular rate and spontaneous circus tachycardia did not occur.

The effects of antiarrhythmic drugs on conduction through accessory atrioventricular pathways and on the induction of tachycardia by atrial or ventricular stimulation have recently been recorded (Wellens and Durrer, 1974; Mandel *et al.*, 1975). This report concerns a patient with pre-excitation and life-threatening atrial arrhythmia. Circus movement tachycardia could be provoked by atrial stimulation only after the administration of procainamide.

Case report

A 57-year-old labourer was seen in January 1969, because of rapid palpitation. There were no significant clinical findings. The electrocardiogram showed sinus rhythm with type B ventricular pre-excitation. The PR interval was 0·08 s and the PS interval 0·22 s. Subsequently the attacks of palpitation were infrequent. Digoxin, 0·25 mg daily, and practolol, 50 mg t.i.d., were started at another hospital in 1973. He then had occasional syncopal attacks: loss of consciousness was brief and often incomplete.

In March 1975, he was admitted as an emergency after an attack. The electrocardiogram showed atrial flutter, rate 270 per minute, usually with 2:1 atrioventricular block and wide QRS complexes. There were frequent brief episodes of 1:1 conduction and it was suspected that prolonged periods with a ventricular rate of 270 were responsible for the syncope. However, monitoring indicated that the spontaneous cessation of paroxysmal atrial flutter or, at times, fibrillation was followed by asystole which was often of sufficient duration to cause loss of consciousness. That digitalis was a factor in causing sinus node dysfunction was proved by withdrawal and subsequent rechallenge with digoxin. Verapamil also delayed recovery (Fig. 1). During sinus rhythm pre-excitation persisted but the PR and PS intervals had increased to 0·13 and 0·24 s.

ELECTROPHYSIOLOGICAL STUDY

Forty-eight hours after the discontinuation of digoxin and practolol, His bundle activity was recorded using a tripolar electrode introduced percutaneously into the left femoral vein. An ink-jet

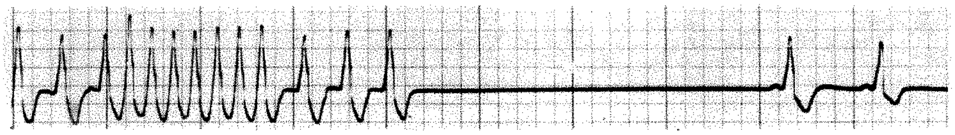

FIG. 1 *Prolonged asystolic pause following cessation of atrial flutter. Treatment: oral verapamil 40 mg t.i.d., a further dose of 6 mg had been administered intravenously 15 minutes before the record.*

recorder was employed and records were made at a paper speed of 100 mm/s. A modified lead II electrocardiogram was recorded simultaneously. Two poles of a multipolar electrode, previously introduced for control of the asystolic pauses, which were in close proximity to the lower part of the lateral wall of the right atrium, were used to introduce bipolar test stimuli at a rate of 40 per minute.

During sinus rhythm, rate 65 per minute, pre-excitation was evident on the body surface lead (Fig. 2A). The PR interval was 130 ms. His bundle deflections were present in the intracardiac lead with a PH interval of 110 ms and an HV interval of 20 ms. Stimuli following 345 ms or longer after the spontaneous P wave were invariably conducted via the accessory pathway, as were three out of three stimuli with intervals of 300 to 305 ms. No stimulus with an interval shorter than 300 ms produced atrial depolarization. Five stimuli following the P wave at intervals of 320 to 340 ms were recorded. Four of the five were conducted to the ventricles entirely via the atrioventricular node. The beat induced by the most premature of these stimuli was followed by a close coupled beat conducted via the atrioventricular node (Fig. 2A). Pure atrioventricular nodal conduction was associated with an HV interval of 35 ms.

Procainamide, 140 mg (2·4 mg/kg), was injected intravenously over a 6-minute period. Right atrial stimulation now frequently caused prolonged episodes of tachycardia (Fig. 2B). During sinus rhythm (rate 65 to 70/min) ventricular aberration was reduced (PR 180 ms, PH 130, and HV 50 ms). Stimuli less than 370 ms after the P wave did not produce atrial depolarization. All 6 stimuli recorded with intervals of 370 to 440 ms induced sustained tachycardia, conducted entirely via the atrioventricular node, at a rate of 120 per minute. The HV interval for beats conducted exclusively via the atrioventricular node was now 60 ms. Tachycardia was repeatedly terminated by single premature stimuli or by trains of stimuli at 220/min (Fig. 2B).

Most test stimuli 500 ms or longer after the spontaneous P wave resulted in aberrantly conducted beats, but on five occasions stimuli at intervals of 500 to 685 ms were conducted entirely by the atrioventricular node, indicating depression of conduction in the accessory pathway throughout the cardiac cycle. None of these stimuli induced tachycardia.

MANAGEMENT

Although procainamide had been associated with the appearance of pacing-induced tachycardia, the clinical problem was one of an uncontrollable ventricular rate during atrial arrhythmia. Treatment with slow release procainamide was started. Procainamide, 4 g per day, was required to control the ventricular rate during attacks (plasma level 3·0 μmol/l (8·1 μg/ml)). On this dosage exclusive antrioventricular nodal conduction during atrial arrythmia was often apparent, the average heart rate was 130 per minute, and very short cycles were absent. Regular narrow complex tachycardia similar to that induced by pacing did not occur. During the 10-month period of follow-up he has been well and has not noticed palpitation.

Discussion

Drugs which block conduction in the accessory pathway, such as procainamide, may prevent the induction of tachycardia in patients with the Wolff-Parkinson-White syndrome. Thus the initiation of tachycardia by premature stimuli was prevented in 6 of 10 patients given procainamide, quinidine, or ajmaline, studied by Wellens and Durrer (1974) and in 6 of 9 patients given procainamide reported by Mandel *et al.* (1975). However, Wellens and Durrer predicted that drugs that selectively prolong the refractory period of the accessory pathway may also widen the range of premature beat intervals at which tachycardia can be initiated. Furthermore, they described 3 patients in whom tachycardia could be induced by critically timed stimulation only after administration of a drug with this effect. In 2 of these patients only ventricular stimulation resulted in tachycardia, and in the third quinidine appeared to permit the initiation of circus movement tachycardia during atrial stimulation by preventing an atrial re-entrant beat from blocking the atrial component of the tachycardia pathway. Four patients in whom tachycardia could not be provoked by the extrastimulus technique were included in the study by Mandel *et al.* (1975). In none of these was the initation of tachycardia after procainamide administration reported.

In this patient, procainamide administration permitted the initiation of tachycardia by premature atrial stimulation. Though re-entry was possible before procainamide was given, the drug widened the range of premature stimulation intervals at which re-entry could be elicited, in association with an increase in the refractory period of the accessory pathway relative to that of the atrioventricular node.

Re-entry involving the accessory pathway is the likely mechanism of the coupled premature beat and episodes of tachycardia after atrial stimulation, since atrioventricular conduction of the initiating and subsequent beats was invariably via the atrioven-

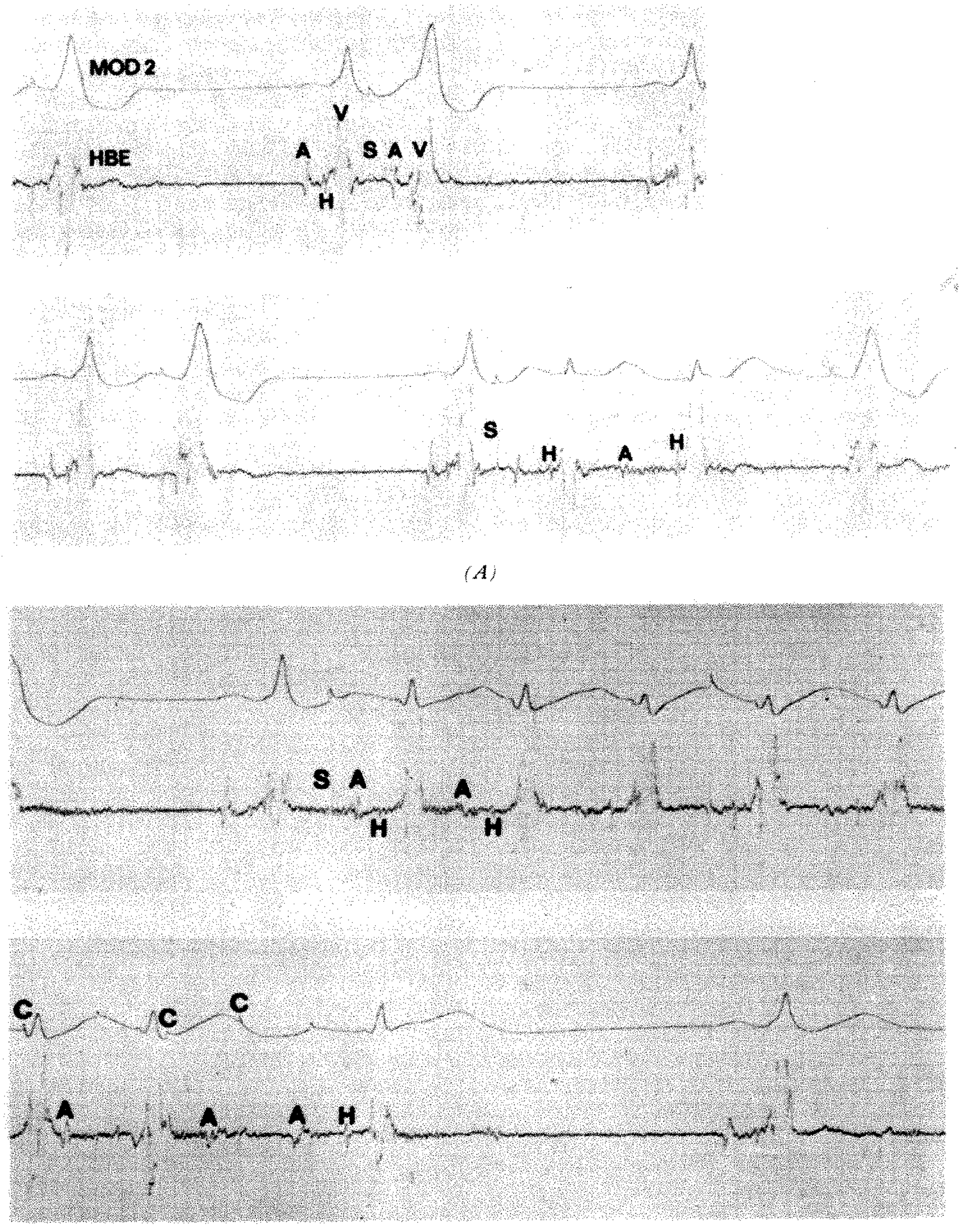

FIG. 2 *His bundle electrograms. (A) Asynchronous atrial pacing at 40/min. Paced beats in upper panel and on left of lower panel are conducted via the accessory pathway and H deflections do not precede ventricular activation. The stimulus on the right of the lower panel (P-to-stimulus 320 ms) induces a beat conducted via the His bundle which is followed by a single, similarly conducted beat. (B) After procainamide 140 mg intravenously. The delta wave is smaller. The stimulus in the upper panel initiates tachycardia during which the ventricles are activated via the normal pathway. Tachycardia was terminated by a series of stimuli at 220/min (lower panel). S = right atrial stimuli; C = stimuli capturing the atria during rapid pacing.*

tricular node. It seems impossible to attribute the different effects of stimulation before and after procainamide to chance variations in the timing of the stimuli. Sustained tachycardia did not occur during several minutes of stimulation at the beginning of the study, yet recurred only seconds after the end of each episode after procainamide administration.

Since the 4 normally conducted beats induced during the control period resulted from stimuli with intervals comparable to those of other beats that were conducted via the accessory pathway, concealed anterograde accessory pathway conduction following these 4 stimuli may have hindered subsequent retrograde conduction, explaining the difficulty in initiating re-entry. In support of the possibility that procainamide abolished concealed anterograde conduction, the ventriculoatrial interval before the first re-entrant atrial complex of induced episodes of tachycardia (265 ms) was shorter than the corresponding interval before the single re-entrant beat elicited before procainamide administration (280 ms), consistent with indirect enhancement of retrograde conduction by the drug.

A low amplitude deflection is apparent on the His bundle lead 155 ms after the onset of the V deflection of the single re-entrant beat (Fig. 2A). Similar deflections occurred following 2 of the 3 other normally conducted beats that did not initiate circus movement tachycardia. If these low amplitude deflections were atrial in origin and resulted from early retrograde conduction in the accessory pathway, failure to establish tachycardia could have been associated with subsequent anterograde block of these premature atrial beats in the atrioventricular node. Slowing of retrograde conduction by procainamide may have delayed the arrival of the impulse at the atrioventricular node until after the end of its refractory period, permitting completion of the tachycardia circuit.

The ease with which the effect of procainamide in facilitating re-entry during atrial stimulation was shown may be explained by the low dose of the drug employed. The patients in the other reported studies received 10 mg/kg compared with 2·4 mg/kg administered to this patient. Higher doses might have prevented tachycardia by blocking retrograde conduction in the accessory pathway.

The contrast between the result of atrial stimulation and that of spontaneous atrial premature beats, and the absence of spontaneous circus movement tachycardia during procainamide therapy require comment. The prematurity of atrial stimuli which induced circus movement tachycardia after procainamide but never induced atrial flutter or fibrillation was comparable to that of spontaneous ectopics which precipitated atrial arrhythmias but never circus tachycardia. The paced region low in the right atrium was probably quite close to the accessory pathway, since regular pacing at a rate slightly faster than the sinus rate was associated with a reduction in the PR interval to 0·08 s. The rapid conduction of a premature stimulus to the adjacent accessory pathway would tend to favour atrioventricular nodal conduction if the bypass were still refractory, and the induction of tachycardia. Spontaneous atrial ectopics may have arisen proximal to a potential atrial re-entry site (e.g. the sinoatrial node) and initiated atrial arrhythmia.

Prolongation of the PR interval with negligible increase in the PS interval occurred during the 6-year period of observation and correlated with the appearance of severe arrhythmias. Disease of the accessory pathway or its atrial connexions may have developed. The appearance of drug-induced sinus node dysfunction supports the latter possibility. Spontaneous arrhythmia is more likely to have been the result of pathological changes in the atria than in the accessory pathway. Though H deflections preceded the delta wave during sinus rhythm, this was not the case during atrial stimulation (Fig. 2A). The accessory pathway, is, therefore, truly atrioventricular, rather than His-ventricular.

The patient was clearly at considerable risk of sudden death. Therapy with procainamide reduced the risk.

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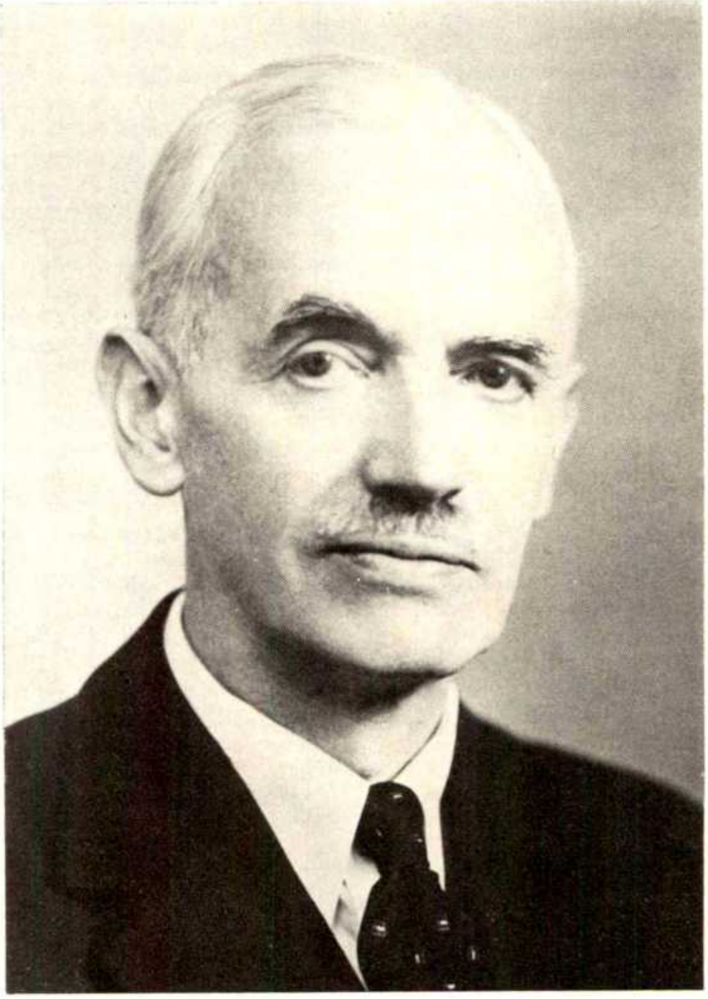
Requests for reprints to Dr. J. S. Geddes, Cardiology Department, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, Northern Ireland.

Memoir

British Heart Journal, 1977, **39,** 334–335

John Crighton Bramwell



John Crighton Bramwell, emeritus professor of cardiology in the University of Manchester and consulting physician to Manchester Royal Infirmary, died on 8 September 1976 at the age of 87. He was one of the small group of physicians who laid the foundations of cardiology as a speciality in Britain; to him the Cardiac Club, the British Cardiac Society, and the *British Heart Journal* meant a great deal and to all these he gave devoted service.

He came from a well-known Edinburgh medical family (his father was Sir Byrom Bramwell and his elder brother the distinguished neurologist Edwin Bramwell). It seemed appropriate that he should go south and, when he left Cheltenham College, he became an Exhibitioner of Trinity College, Cambridge and, in 1910, graduated Bachelor of Arts with first-class honours in the Natural Science Tripos. The following year he devoted to research with Keith Lucas with whom he published his first paper (on the refractory period in nerve) in the *Journal of Physiology*. He had already decided to spend his professional life in Manchester on the basis, he said, that at that time it had the largest population within the sphere of influence of any single medical school in Britain, and, therefore, offered the best opportunity for the development of the then-young speciality of cardiology, to which he had already decided to devote himself. In 1912 he was awarded a Graduate Entrance Scholarship to the Manchester Medical School and began his clinical studies. In 1914 he volunteered for military service, and in 1915 was given two months' leave to sit his final examinations. He then went to France with the 23rd Division and served until the end of the war. Back in Manchester, after a period as house physician at the Manchester Royal Infirmary he was appointed Medical Registrar in 1919 and the following year took charge of the newly-formed Electrocardiographic Department. The next four years were devoted to clinical teaching and to experimental research with A. V. Hill. In 1923 he was awarded a gold medal for his M.D. dissertation, and elected one of the first four Rockefeller Travelling Fellows. During the same year he became the first elected member of the Cardiac Club (founded the previous year). He held the post of secretary from 1928 to 1932; he was chairman in 1931 and again in 1937, when he presided at the meeting which changed the Cardiac Club into the British Cardiac Society. He was chairman of the Society in 1955 and was elected an honorary member. He constantly supported the *British Heart Journal*, he was a member of the Editorial Board, and made many contributions to its pages. On the occasion of his election as an Honorary Member of the Society, the members dedicated a number of the Journal to him; in that issue Maurice Campbell wrote an appreciation of his contributions to cardiology.

During his year in the United States as Rockefeller Fellow he worked in Joseph Erlanger's laboratory at Washington, St. Louis, at the Rockefeller Institute for Medical Research in New York, and spent two months visiting the principal medical centres in the United States and Canada. In 1926 he was appointed to the staff of the Manchester Royal Infirmary. In 1946 the Electrocardiographic Department was incorporated into the new University Department of Cardiology, in a new building, and he was director of this department until he retired in 1954. From 1940 until 1946 he held the post of part-time Professor of Systematic Medicine; the chair then became whole-time, and he was appointed to a personal chair as Professor of Cardiology, the first such chair in this country. He continued his interest in general medicine, however, for he maintained that cardiology could be practised wisely only with a continuing background knowledge of general medicine.

From 1911 to 1954 he made important contributions both to the physiology of the circulation and to clinical cardiology. He was never more happy than with a small group of students at the bedside, and he was in great demand both as a lecturer and as an examiner. It would be impossible here to enumerate the many distinguished lectures he gave or the range of his research work, or his many other activities in the Royal College of Physicians, the Association of Physicians, and elsewhere. He published 9 books and some 70 papers. His work on the transmission of the arterial pulse and arterial elasticity, his contributions to the study of heart disease in pregnancy, and to the features of the circulation in athletes are well known. But his interests ranged much more widely, and he was always as interested in his patients as in their diseases.

A factual summary of even so distinguished a career does less than justice to the man. I knew him as his patient, assistant, colleague, and successor; in all these situations Crighton Bramwell exemplified for me many admirable qualities: sympathy, devotion, skill, wisdom, and integrity, but he possessed one gift that enabled all his other qualities to fructify richly: the art of advocacy, most essentially in what Lord Birkett once described as 'the art of attractive and persuasive speech on all occasions that call for its exercise' adding 'but the price to be paid is one of taking pains and exercising much patience'. Bramwell's mastery of this art is evident even in his writings, but his spoken word added the charm of his personality, the restraint of his character, and a speaking voice of persuasive clarity and distinction. His easy use of graceful and simple English played a most significant part in all aspects of his life, whether as physician, mentor, examiner, lecturer, colleague, host, or friend. It allowed the effective expression of his wisdom, understanding, and sympathy; it made his bedside teaching and lectures an invariable pleasure to his audience, and it gained him the willing collaboration of his colleagues in those well-conceived projects to which he had set his mind. He maintained the highest standards of professional and personal integrity, yet rarely criticised others and then only by a rather pointed omission to praise. Inevitably, he set an example hard to follow, but few who knew him will fail to carry his principles and standards as a model, perhaps impossible to achieve but always worth the striving.

A. MORGAN JONES

Correspondence

British Heart Journal, 1977, **39**, 336–337

Electrocardiographic antecedent of primary ventricular fibrillation

Sir,

We read with interest the study of El-Sherif *et al.* (*British Heart Journal*, 38, 415) and wish to comment on some aspects of their 2-year study on 450 patients with acute myocardial infarction.

Firstly, the mean time delay between onset of symptoms and onset of electrocardiographic monitoring was 4 hours. This is itself an excellent achievement but means that the majority of patients with primary ventricular fibrillation with a peak incidence within 1 hour after onset of symptoms are excluded. Rather patients with late primary ventricular fibrillation were studied (Lovell and Prineas, 1971; Gordon and Kannel, 1971; Oberman *et al.*, 1975).

Secondly, the electrocardiogram was continuously and visually monitored in all patients but only in 'several' of the 450 patients was it continuously recorded on magnetic tape for the first 24 hours in the CCU. We believe, as do others (Ryden *et al.*, 1975), that continuous visual electrocardiographic monitoring is less effective than continuous electrocardiographic recording in detecting minor ventricular conduction changes, isolated premature beats, short lasting arrhythmias, progressive increase of heart rate, and other changes. No information is given about the alarm period (see later), which could be important in a negative study. Continuous electrocardiographic recording (as opposed to monitoring) could at least reduce the observed group of patients with primary ventricular fibrillation who were thought not to have warning arrhythmias.

Thirdly, the use of lignocaine does not prolong the QT interval significantly and probably did not alter the prematurity index of the remaining premature beats. But lignocaine probably suppressed multiple myocardial ectopic foci and eliminated or filtered premature ectopic beats and arrhythmias with unknown prematurity index, ventricular conduction, and frequency of appearance.

Fourthly, a crucial parameter concerning warning arrhythmias was not taken into consideration. Each chosen arrhythmia or electrocardiographic sign has a variable predictive value and a limited time for which there is an increased risk of onset of primary ventricular fibrillation. The increased risk of primary ventricular fibrillation remains for the determined time after the appearance of a warning arrhythmia and is gone when this determined period expires. This means that the 'alarm period' of increased risk of primary ventricular fibrillation has to be set in a patient with acute myocardial infarction according to the determined warning times of each chosen warning arrhythmia or sign. Our data on the 'alarm period' in baboons (Bruyneel and Opie, 1973) could be reconciled with those of El-Sherif *et al.* (1976) if it were assumed that the R-on-T phenomenon was more lethal during the first hour after the onset of acute myocardial infarction than 4 hours or more after.

In conclusion, warning arrhythmias and signs should be selected and defined in precise conditions. The 'alarm period' of each should be known, together with the predicted incidence of ventricular fibrillation. Drug treatment should not be used in such studies which should have continuous electrocardiographic recording and should specify whether the primary ventricular fibrillation was early or late. A study which came close to these criteria was published recently by Lie *et al.* (1975), however, without analysing the warning time of each of their chosen warning arrhythmias and electrocardiographic signs. The observation of El-Sherif *et al.* (1976), that the ventricular vulnerability period extends beyond the QT intervals at least 4 hours after onset of symptoms, needs further evaluation.

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This letter was shown to Dr. El-Sherif and his colleagues, who comment as follows:

(1) Lignocaine was given only to patients who showed warning arrhythmias. Thus, the use of the drug would not affect the incidence of warning arrhythmias in the whole group.

(2) The concept of the 'alarm period' reported by Bruyneel and Opie (1973) based on their observations in baboons with acute myocardial infarction is interesting. However, to the best of our knowledge, it was not confirmed in clinical studies or in studies dealing with acute myocardial infarction in the dog, including several of our experimental studies. We think that the problem with this and similar concepts including the R-on-T phenomenon is that they depend heavily on certain electrocardiographic configurations to make certain predictions without an adequate understanding of basic electrophysiological mechanisms. Indeed, the major theme of our study was to present an assessment of the R-on-T phenomenon in acute myocardial infarction that would provide a clinical correlation to our previous experimental observations. In a clinical paper the discussion of basic mechanism was understandably restrained. However, the analogy drawn in clinical electrocardiography between ventricular tachyarrhythmias induced by a single test stimulus applied during the relative refractory period (Wiggers and Wegria, 1940) and spontaneous ventricular tachyarrhythmias ushered by an early coupled premature beat was probably unwarranted. For the analogy to be more accurate, one has to visualise the first early coupled premature beat as an intruder suddenly introduced by firing of an automatic focus early in diastole which provokes a possible re-entrant ventricular tachyarrhythmia. This situation may very well take place in the intact heart and is indeed closely simulated when the early coupled premature beat is of supraventricular origin. However, there is the real possibility that the first early coupled ventricular premature beat is part and parcel of the same electrophysiological process that underlies the ventricular tachyarrhythmia that follows. Assuming that the tachyarrhythmia is based on re-entry, it becomes necessary to explain why the first re-entrant beat has a short coupling interval. A shortly coupled re-entrant beat was explained by a mechanism of focal re-excitation (Han, 1969), by electrotonic shortening of action potentials proximal to the site of unidirectional block (Sasnyiuk and Mendez, 1971), and by shortened recovery in some areas of the myocardium (Geddes *et al.*, 1974). The role any of these mechanisms plays in the intact heart is yet to be determined. However, our recent experimental observations (El-Sherif, Scherlag, and Lazzara, unpublished data) have illustrated an interesting mechanism for re-entrant beats with very short coupling based on considerably delayed activation by the beat before the one to which the premature beat is apparently coupled. In this case, the short coupling will be, in fact, more of an illusion created by the acknowledged deficiency of clinical electrocardiography. This, and similar basic observations are always required to arbitrate the often heated controversies created by studies based on deductive analysis of the electrocardiogram.

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Correspondence

British Heart Journal, 1977, **39**, 338-339

Torsade de pointes

Sir,

In an Editorial (*British Heart Journal*, 1976, **38**, 117) the authors recommend intravenous isoprenaline infusion as the first step for the treatment of *torsade de pointes* ventricular tachycardia. This has the theoretical basis of shortening the repolarisation time and thus avoiding a state of asynchronous depolarisation. Drugs which increase the repolarisation time, such as quinidine, are not only not indicated for the treatment of the above arrhythmia, but can induce it. Though, theoretically, isoprenaline is an ideal agent, there is a risk of inducing ventricular arrhythmias, especially in patients with myocardial ischaemia. This may also occur with the slight increase of the optimal serum concentration of the drug. On the other hand, isoprenaline as a beta-adrenergic stimulant can induce the side effects of sympathomimetics.

Torsade de pointes ventricular tachycardia has been observed (Kounis, 1976) in a patient on prenylamine who was suffering from syncopal attacks and who was given slow release isoprenaline hydrochloride tablets (Saventrine 30 mg t.i.d.) by his general practitioner because he was thought to have Adams-Stokes attacks. Though prenylamine had been discontinued, the patient continued to have syncopal attacks while he was taking Saventrine for the next 7 days. After his admission he was found to have *torsade de pointes* ventricular tachycardia with prolongation of the QT interval. This was attributed to Saventrine because sometimes sympathetic stimulation prolongs the QT interval (Yanowitz *et al.*, 1966). Mexiletine, however, might be a good and effective first step and if isoprenaline is preferred, cardiac pacing must always be instituted simultaneously.

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Yanowitz, F., Preston, J. B., and Abildskov, J. A. (1966). Functional distribution of right and left stellate innervation to the ventricles: production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone. *Circulation Research*, **18**, 416-428.

This letter was shown to Drs. Krikler and Curry who reply as follows:

Sir,

Dr. Kounis quite properly raises queries about the management of this disorder. In our Editorial (Krikler and Curry, 1976) we mentioned its rarity in cardiac ischaemia, citing the explanation offered by Puech (1974); when it occurs in this setting it may well be the result of complicating paroxysmal atrioventricular block (Chiche *et al.*, 1974), and we wonder whether this, or sinoatrial block aggravated by prenylamine (Evans, 1975) was a factor, in addition to the direct effects of prenylamine on repolarisation.

Failure to respond to oral isoprenaline does not mean that this agent directly aggravated the situation: indeed, its effect in accelerating the heart rate and shortening the QT interval may have been inadequate. While the QT interval may be prolonged by the *rapid* intravenous injection of isoprenaline, it is shortened by *infusion* (Abildskov, 1976), a paradox explored in this recent paper. Thus our therapeutic advice is not contradicted by the continuation of the work quoted by Dr. Kounis (Yanowitz *et al.*, 1966). We agree with the inference that pacing may be preferable, but this may not necessarily be available where the patient presents, and, if underlying factors (other than heart block) remain uncorrected, *ventricular* pacing may actually induce *torsade de pointes* (Evans *et al.*, 1976).

Mexiletine has indeed proved useful in the prevention of recurrent *torsade de pointes* after the precipitating factors had been treated (Curry *et al.*, 1976); perhaps it suppresses extrasystoles that could initiate episodes. We have, however, seen three further cases where it occurred when lignocaine was infused after myocardial infarction in patients who had become hypokalaemic because of vigorous diuretic therapy. Under other circumstances the infusion of lignocaine or mexiletine may well help the occasional case, but the value of treatment with intravenous isoprenaline and of atrial pacing has been shown (Slama *et al.*, 1973).

Dennis Krikler and Paul Curry,
Division of Cardiovascular Disease,
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Notice

Symposium on Echocardiography

A Symposium on echocardiography with Doppler applications and new developments will be held 23/24 June 1977 at Erasmus University, Rotterdam, Netherlands.

For further information write to:

N. Bom,
Erasmus University,
P.O. Box 1738,
Rotterdam,
The Netherlands.

British Heart Journal, 1977, **39**, 340–356

Proceedings of the British Cardiac Society

THE AUTUMN MEETING of the British Cardiac Society was held at Imperial College, London, on Thursday and Friday 4 and 5 November 1976. The President, W. SOMERVILLE, took the Chair during the private business. At the scientific sessions the Chair was taken by J. P. SHILLINGFORD. The three finalists in the competition for the Young Research Workers' Prize were Angela J. Drake, M. Afzal Mir, and Andrew P. Selwyn. The Prize was won by M. Afzal Mir. Special symposia were chaired by H. WATSON, M. F. OLIVER, and L. ABRAMS.

Abstracts of Papers

Left ventricular wall thickness changes in normal subjects and patients with ischaemic heart disease

D. G. Gibson, T. A. Traill, and D. J. Brown
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In order to assess changes in left ventricular wall thickness, angiograms were digitised frame by frame from 10 normal subjects and 20 patients with anterior wall motion abnormalities caused by ischaemic heart disease. The timing of changes in wall thickness was compared with those of cavity area. In normal subjects, peak systolic rate of increase of wall thickness was 8·5 ±3 cm/s, and of reduction during filling 10·5 ±4 cm/s. Changes were synchronous with those in cavity area, in that the onset of wall thickening coincided with that of ejection, and peak wall thickness corresponded with minimum cavity area (±20 ms). During isovolumic relaxation, wall thickness fell by 3 ±2 mm before mitral valve opening, and rapidly thereafter until the end of the rapid filling period. In patients with ischaemic heart disease, anterior wall hypokinesis was associated with reduced rate and amplitude of wall thickening, as well as delayed onset. During isovolumic relaxation, major abnormalities of wall dynamics were observed, leading to significant changes in left ventricular cavity configuration. These latter were related to the pattern of coronary arterial involvement. In summary, changes in wall dynamics during systole and particularly during isovolumic relaxation can be used to detect localised abnormalities of left ventricular function.

Abnormal wall movement in left ventricular aneurysm

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It is widely held that the primary abnormality in left ventricular aneurysm is abnormal outward wall movement during ejection. Using a comprehensive computer display, analysis of left ventricular cineangiograms from 40 patients with surgically confirmed aneurysms showed that any such systolic outward movement was unusual and of low amplitude. The most conspicuous abnormalities occurred during the isovolumic periods in the regions of 'good' myocardial function. Between end-systole and angiographic mitral valve opening there invariably occurred abnormal outward movement of those regions of wall at the base exhibiting the greatest overall excursion. This was confirmed by echocardiography in 15 patients who showed a mean increase of dimension before the O point of the apex cardiogram of 71 per cent of the total, compared with 21 per cent in normals ($P < 0{\cdot}001$), and delay in mitral valve opening by 60 ms ($P < 0{\cdot}01$). In isovolumic contraction, particularly in patients with more diffuse disease, echocardiograms showed abnormal inward movement (mean 38% of total excursion, normal 6%, $P < 0{\cdot}01$), indicating asynchronous onset of contraction, also confirmed by angiographic plots. In summary the most characteristic wall movement abnormalities in left ventricular aneurysm occur in the isovolumic periods and their identification may prove valuable in preoperative assessment. 'Typical aneurysmal behaviour' is rare.

Echophonocardiographic assessment of right ventricular contraction in right bundle-branch block

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The relation between electrical and mechanical events of the cardiac cycle was studied in patients with right bundle-branch block. Using simultaneous high resolution echo and phonocardiography, the time intervals from mitral to tricuspid valve closure (Mc-Tc) and from tricuspid closure to full opening of the pulmonary valve (Tc-Po) were measured in 15 patients and in 20 normal controls. Six patients with a normal Tc-Po interval had a Mc-Tc of between 52 and 66 ms, all exceeding the normal range of 12 to 50 ms. In 9 patients Tc-Po exceeded the normal range of 30 to 57 ms and in 4 of these Mc-Tc was also prolonged.

Thus, the electrocardiographic appearance of right bundle-branch block may be associated with:

(a) Delayed onset of right ventricular contraction, shown by long Mc-Tc and wide splitting of first heart sound.

(b) Normal onset, but reduced velocity of right ventricular contraction, shown by long Tc-Po but normal Mc-Tc and normal first heart sound.

(c) Both delayed onset and reduced contraction velocity.

It is suggested that the variable patterns of contraction correspond to different sites of conducting system disease; late onset indicating proximal damage and reduced velocity indicating 'arborisation block' analogous to that described for left bundle-branch block.

Cross-sectional echocardiography in mitral prolapse

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Infirmary; Department of Clinical Physics and
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Multiple beam cross-sectional echocardiograms were recorded in 13 patients with clinical and single beam echocardiographic findings consistent with mitral prolapse.

Cross-sectional scanning showed mitral prolapse in all 13 patients and allowed 3 groups to be defined.

1. In 7 patients the mitral anterior leaflet was elongated and the chordae to it were slack; the anterior leaflet impinged on the interventricular septum in diastole and in systole formed an arc in the left atrium, making contact with its posterior wall close to the atrioventricular junction.
2. In 3 patients the anterior leaflet appeared thickened and possibly folded; it did not impinge on the septum in diastole and systolic prolapse was into the upper part of the left atrium.
3. In 3 patients both leaflets appeared elongated; in diastole both were abnormally mobile and in systole both prolapsed and were widely separated. Some features of the conventional echocardiogram in mitral prolapse were explained by the cross-sectional scans and by single element selection from them.

It is concluded that the extent and mechanism of mitral prolapse can be seen by cross-sectional echocardiography which thus has advantages over the single beam method in the investigation of this disorder.

Diastolic function in hypertrophic cardiomyopathy

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Hospital, London, and Cardiac Department, Brompton
Hospital, London

Frame by frame analysis of left ventricular angiograms of 20 patients with hypertrophic cardiomyopathy (HCM) and 10 normal subjects has been performed. In the patients with HCM the diastolic peak rate of change of volume (772 ± 263 cm^3 s^{-1}), the peak rate of increase of a transverse dimension placed above the level of the papillary muscles ($18{\cdot}7 \pm 5{\cdot}3$ cm s^{-1}) and the mean filling rate during the rapid filling period (542 ± 204 cm^3 s^{-1}) were not significantly different from normal. The isovolumic relaxation period (IRP) (140 ± 38 ms) was significantly longer than normal (93 ± 14 ms) and was inversely correlated with the peak rate of diastolic filling ($r = 0{\cdot}7$, $P < 0{\cdot}01$). Wall movement during this period was symmetrical in contrast to patients with ischaemic heart disease.

An echocardiographic study of 45 patients with HCM has confirmed these findings. The peak rate of increase of dimension during diastole was normal ($13{\cdot}4 \pm 6{\cdot}1$ cm s^{-1}) and the onset of anterior mitral valve movement, normally synchronous with minimum dimension (1 ± 6 ms), was significantly delayed (76 ± 37 ms).

In order to reconcile the finding that diastolic filling proceeds at a normal rate in HCM with the known abnormalities of left ventricular stiffness, a concept was discussed which proposes that early diastolic filling is mediated predominantly by a shape change rather than passive distension of fibres. This concept of filling was further substantiated by simultaneous left ventricular dimension-pressure studies.

Studies of systolic and diastolic function in cardiac amyloidosis

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Cardiac function has been studied in 5 patients with cardiac amyloidosis diagnosed by endomyocardial biopsy. Systolic function was normal in 3 cases as assessed by cardiac index, ejection fraction from left ventricular cineangiography, and force velocity analysis. This diastolic dip and plateau wave form was a characteristic but not invariable finding: it being absent in the case where biopsy also showed extensive fibrosis.

The diastolic pressure-volume relation was studied in 2 cases of cardiac amyloidosis. High ventricular end-diastolic pressure but normal end-diastolic volume indices in all cases implied a disorder of diastolic compliance. The diastolic pressure volume plots suggested a sudden decrease in distensibility with normal early filling of the ventricle.

Electron-microscopy was the most reliable way of making the diagnosis on the endomyocardial biopsy specimens, especially in the presence of fibrosis. It is not valid to assume the diagnosis of cardiac amyloidosis from the finding of amyloid in other organs. This was illustrated by a sixth patient with familial amyloidosis and coronary artery disease but a normal cardiac biopsy, whose diastolic pressure volume plot was in distinct contrast to the 2 cases of cardiac amyloidosis studied in this way.

Formes frustes of Marfan's syndrome presenting with severe aortic regurgitation—a clinicogenetic study of 18 families

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Eighteen patients presenting with severe aortic regurgitation and dilatation of the ascending aorta were found, after histological examination, to be *formes frustes* of Marfan's syndrome. All these cases had aortic valve replacement with graft reconstruction of the ascending aorta, and formed the basis of this study.

Of 126 first degree relatives, 85 were living and 67 (78·8%) examined. None had the classical clinical features of Marfan's syndrome but stigmata of the disease were found in 25 (37·3%) of the 67 examined, which involved 12 of the 18 families studied.

Using strict diagnostic criteria, cardiovascular abnormalities affecting the aortic valve or wall were present in 6 (9·0%). One or more skeletal index (height-span difference, metacarpal index, phalangeal index) was present in 18 (26·9%), and ocular abnormalities in 5 (7·5%). In 4 relatives, abnormalities involved more than one system.

The practical importance of making the correct aetiological diagnosis lies in the increased operative hazards of cardiovascular surgery in Marfan's syndrome. This work emphasises the value of family studies when dealing with isolated aortic regurgitation of obscure aetiology.

Cardiovascular abnormality in homozygous familial hypercholesterolaemia

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Eight patients with homozygous familial hypercholesterolaemia have been studied. There were 4 male and 4 female patients whose ages ranged from 10 to 40 years. All showed hyper betalipoproteinaemia and their untreated cholesterol levels ranged from 14 to 28 mmol/l (540 to 1080 mg/100 ml). Deforming xanthomata developed between the ages of 3 and 15 years and these were the presenting features in every instance. Every patient also showed a corneal arcus.

The cardiovascular features were similar in each patient. All had signs of aortic stenosis with accentuated aortic valve closure sounds but no ejection click. Peripheral arterial bruits were common. Five patients showed voltage changes of left ventricular hypertrophy with ischaemic changes in the electrocardiogram in 4. These 4 patients had angina and 2 patients without angina showed evidence of ischaemia or past infarction on the electrocardiogram.

Echocardiograms available in 4 showed multiple dense echoes from the aortic valve together with thickening and narrowing of the aortic root. Left heart catheterisation in 4 showed a characteristically deformed aortic root. This was narrowed and irregular but the abnormality terminated abruptly 5 to 7·5 cm above the aortic valve. Narrowing of one or both coronary ostia and an aortic valve gradient of between 30 and 40 mmHg was shown in all 4 patients catheterised.

Three patients died suddenly and necropsy which was available in 2 showed the oddly sited atheroma which in this condition affects a part of the aorta which is usually spared. Thick projecting cushions of atheroma were confined to the proximal aortic root, narrowing the coronary ostia and interfering with opening of the aortic valve. It seems that coronary ostial stenosis may be responsible for the early unexpected deaths known to occur in these subjects.

Non-selective timed pulse coronary xerography

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Selective coronary arteriography provides high definition images of the major coronary arteries. The technique has two major disadvantages. Intubation of the coronary ostia is not without risk and selective dye injection can lead to cardiac arrhythmias. There is a great need for a new technique, with equal or better definition, which does not require selective intubation, and which carries less risk of arrhythmias.

Xerography is particularly suited to angiography on account of specific edge enhancement with a low dose of radio-opaque medium. An image is created on an electrostatically charged metal plate coated with selenium. Local charge differences depend on x-ray energy in analogy to the chemical changes produced in silver halide film emulsion. The charged plate is developed by blowing powder over the surface in a special chamber —and is then photographed. This procedure takes approximately 2 minutes.

Opacification of the coronary arteries can be achieved adequately by powered pump injection into the aortic root given certain provisions. A special spray catheter is required. Coronary filling occurs maximally in early diastole and opacification is optimum when the injection is timed to coincide with coronary flow. Repetitive pulses help to fill the arteries throughout the whole length. The x-ray tube is timed to fire at the end of diastole—so exposing the selenium sheet at the moment of complete coronary filling.

Salient points in the development of coronary xerography were discussed, together with illustrations.

Assessment of myocardial perfusion in chronic stable angina and CABG patients using thallium-201

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The radioactive monovalent cation thallium-201 (^{201}Tl) is a suitable imaging agent for external detection with a gamma camera and is an accepted analogue of potassium (Strauss *et al.*, 1975; Gehring *et al.*, 1967). It is currently being assessed as an indicator of myocardial perfusion, 'cold' spots in the myocardial scintillogram representing regions of ischaemia or necrosis.

The present study was undertaken to evaluate the diagnostic potency of thallium scintillography in detecting myocardial ischaemia or necrosis in a group of patients with chronic stable angina and to assess the efficacy of coronary bypass grafting operations in improving ischaemic myocardial segments.

Each patient performed an exercise test and received 1·5 mCi of ^{201}Tl intravenously at the peak of angina, exercise continuing for 30 seconds after injection. Myocardial images were obtained in 4 projections immediately after exercise and analysed on a regional basis using a computer.

Twenty patients with normal coronary arteries shown by angiography were studied in a similar fashion and compared with 150 studies in 100 patients, 15 of whom were analysed before and after CABG.

The technique is highly reproducible, more sensitive, and more precise in lesion localisation than the exercise electrocardiogram and is capable of showing changes in perfusion that make it valuable in the follow-up of CABG patients.

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Closed chest left main coronary artery perfusion in study of heart function

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Experimental analysis of heart function and performance in a closed chest situation is often incomplete on account of the difficulty in continuously measuring and controlling coronary blood flow and oxygen consumption. We have devised a new technique whereby the left main coronary artery is intubated under *x*-ray control and sealed off from aortic blood—so allowing perfusion from a pressure controlled external source. By catheter sampling of blood from the great coronary vein, the oxygen consumption of the left ventricle can be derived and the values compared when the left ventricle operates under different mechanical conditions. With the aid of an intraventricular micromanometer, a previously implanted aortic root flowmeter, and other instrumentation, a comprehensive knowledge of heart action may be correlated with coronary vascular resistance and coronary flow. Thus the effects of drugs on the economics of heart function may be better assessed.

Regional pulmonary oedema: assessment by chest radiograph, perfusion lung scan, and isotope double indicator-dilution

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The chest radiograph is routinely employed for the assessment of pulmonary oedema. Ideally, therefore, it should be sensitive to both the presence and severity of oedema. In order to investigate this, we have used a new double indicator-dilution technique for the estimation of regional extravascular lung water (RELW) to study 15 patients (3 twice) with chronic left heart disease. By monitoring with external counters the passage of two gamma-emitting isotopes (^{113m}In and $H_2{}^{15}O$) through the upper and lower zones of the right lung, RELW has been calculated from the difference in mean transit times. An erect chest radiograph and ^{99m}Tc lung scan were also performed. These were graded for the degree of upper zone blood flow diversion. The severity of interstitial or intra-alveolar oedema was also assessed on the radiograph.

In 14 of the 18 isotopic studies, RELW was raised indicating pulmonary oedema. Oedema was detected in the radiograph on only 6 of these occasions. The severity of oedema was not assessed accurately from the radiographs. On 13 occasions when there was pulmonary oedema, upper zone blood flow diversion was present on both radiograph and lung scan. Blood flow diversion is, therefore, a sensitive index of mild pulmonary oedema.

Evaluation of beta blockade, bendrofluazide, and prazosin in severe hypertension

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Nineteen patients with severe hypertension were studied in a clinic set aside for the purpose. All blood pressures were taken by the same two observers using the London School of Hygiene and Tropical Medicine sphygmomanometer. Heart rates were counted on every occasion. Before treatment average supine blood pressures in the 19 were 211/123 mmHg.

These patients were selected for the study as beta blockade alone failed to lower blood pressure adequately.

The addition of bendrofluazide to beta blockade produced an average further fall in mean blood pressure of 11 per cent supine, 13 per cent erect. The full effect was apparent at 2 weeks and there was no difference between 5 and 10 mg daily. Serum, urine, and dietary potassium were monitored.

The addition of the reputedly vasodilator drug, prazosin, either 2 or 5 mg three times daily to beta blockade produced an average further fall in mean blood pressure of 13 per cent supine and 16 per cent erect.

Adding prazosin to beta blockade produced an additional fall in heart rate which reached statistical significance in the supine position. From this we deduce that the drug has other actions than peripheral vasodilatation.

In 10 of the 19 patients neither bendrofluazide nor prazosin added to beta blockade lowered blood pressure to normal and these 10 were given all three drugs simultaneously. The final results in 18 patients (one withdrawn) gave average blood pressures of 155/94 supine, 139/93 erect and 140/91 mmHg post exercise. Side-effects were recorded by questionnaire at each visit.

This combination of treatments promises control of blood pressure in the more severe hypertensives, with few side-effects, using no more than six tablets daily.

Direct arterial blood pressure with electrocardiogram in ambulant hypertensives treated with post-ganglion sympathetic blocking drugs

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The direct arterial blood pressure and electrocardiogram of 6 patients taking bethanidine, 4 taking guanethidine, and 1 taking debrisoquine, all as chronic therapy, were recorded continuously for up to 24 hours. All were poorly controlled on clinic blood pressure recordings and 2 had symptoms of postural hypotension. All patients showed severe postural changes in arterial pressure during the day with resting pressures all greater than 185/95 mmHg falling to less than 130/70 mmHg. The mean fall of systolic pressure was 125 (SD ±31) mmHg, and diastolic pressure 63 (SD ±15·5) mmHg; in 3 patients the postural drop was associated with ST changes on the electrocardiogram. The mean pressures during the day and night were computed and showed no significant difference in the postural hypotensive effect of the drugs. All three act mainly by decreasing venous return to the heart which explains this finding. In view of this severe postural hypotensive action these drugs should not now be considered in the treatment of hypertensives, particularly those with evidence of myocardial ischaemia or cerebrovascular insufficiency.

Relation between baroreceptor nerve activity and carotid sinus dimension in the dog

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Plots of pressure-firing rate from carotid baroreceptors show a linear relation followed, at higher pressures, by a plateau with no further increase in nerve discharge. Previously this has been attributed to properties of the neural elements rather than to a mechanical limit to wall deformation (Koushanpour and Kelso, 1972).

We have re-examined this by measuring carotid sinus dimension with an ultrasound transit time technique (Bertram, 1974) simultaneously with nerve activity.

When nerve firing is related to dimension we found, contrary to Koushanpour and Kelso, a linear relation over the whole range of intrasinus pressures studied (40→240 mmHg).

Simultaneous comparisons of the mechanical properties of the sinus with the adjacent carotid artery have shown that the sinus wall is composed of stiffer material than the more muscular artery, but because it is thinner it is more distensible. The sinus wall follows mechanical events more rapidly than the artery and is very much less influenced by circulating catecholamines. Thus we have found that carotid baroreceptors behave as linear stretch receptors over the whole range of pressures likely to be found *in vivo*.

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Diagnosis and sizing of acute myocardial infarction: comparison of radionuclide, electrocardiograph, and enzyme measurements

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Fifty patients with suspected acute myocardial infarction had serial electrocardiograms, enzyme measurements, and scintigraphy using ^{99m}Tc pyrophosphate. Forty-four patients with various cardiac disorders had ^{129}Caesium scans and electrocardiograms.

Positive pyrophosphate scans were obtained in 9 of 18 patients without positive electrocardiograms and in 7 of 12 without an enzyme rise. Negative pyrophosphate scans were obtained in 5 of 41 patients with positive electrocardiogram or enzymes.

Using computer stored images, estimates of infarct size were obtained from pyrophosphate and caesium scans. Both were compared with infarct size from the 12 lead electrocardiogram. Infarct size from caseium scans correlated better with the electrocardiogram than did that from pyrophosphate scans. The pyrophosphate scans were further compared with peak enzyme levels, infarct size correlating better with the MB fraction of CK ($r=0{\cdot}90$) than with total CK ($r=0{\cdot}54$), SGOT ($r=0{\cdot}45$), or SHBD ($r=0{\cdot}34$).

Pyrophosphate scans are useful in the diagnosis of acute myocardial infarction especially when the electrocardiogram is negative or obscure and, since they correlate with peak enzyme levels, in estimating the size of recent infarction. Caesium scans correlate better with the electrocardiogram as they reflect the remaining viable myocardium. The combined use of caesium and pyrophosphate scans give more complete information than either alone.

Measurement of peak instantaneous power delivered by left ventricle to aorta: sensitive index of myocardial responsiveness in coronary artery disease

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Descriptions of the contractile behaviour of the heart as a muscle on the one hand or as a pump on the other artificially separate conceptual dimensions, because the aggregated behaviour of individual muscle fibres together constitutes the whole organ, which can than be described as a pump. It is, therefore, logical to study the integrated behaviour of the heart by measuring its power output. This is a composite description of the pressure and flow it generates, incorporating all its mechanical activities simultaneously, including those dependent on external factors controlling its function. Fifteen patients with coronary artery disease and restricted exercise capability were studied using a special catheter. Blood velocity in the aorta and pressures in the left ventricle and aorta were measured simultaneously. Instantaneous power delivered to the aorta was computed from data obtained at rest and after graded isoprenaline. The studies suggest that response to coronary artery surgery depends as much on the heart's ability to respond to increased load as upon increased blood supply.

Myocardial response to inotropic stimulus was better estimated from peak hydraulic power measurements than by any other currently available estimate of ventricular function.

Effect of light dynamic exercise on catecholamine concentrations in coronary circulation of man

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Dynamic exercise is associated with increased sympathetic activity which may be related to arrhythmias occurring during exercise, particularly in patients with ischaemic heart disease. Since sympathetic stimulation in animals increases catecholamine efflux from the heart, as measured in the coronary sinus, we attempted to assess how autonomic activity affected catecholamine concentrations in the coronary sinus in man, by measuring arterial and coronary sinus catecholamine concentrations, in 7 patients during light, supine dynamic exercise.

Arterial concentrations increased from 1·77±0·53 nmol/l (±SEM) at rest to 2·95±0·65 nmol/l on exercise ($0{\cdot}05>P>0{\cdot}01$), and coronary sinus concentrations from 2·78±0·53 nmol/l at rest to 4·43±0·71 nmol/l on exercise ($0{\cdot}05>P>0{\cdot}01$), consistent with increased sympathetic activity. Since autonomic blockade may also effect the release of catecholamines, the study was repeated following 1·8 mg atropine and 0·2 mg/kg oxprenolol in 6 patients, though only the coronary sinus increase was statistically significant (one-tailed test; $0{\cdot}05>P>0{\cdot}01$), the resting concentration of 2·54±0·59 nmol/l increasing to 4·44±1·3 nmol/l on exercise.

Thus light dynamic exercise increases the efflux of catecholamines from the heart which appears to remain unaffected by autonomic blockade.

Systolic pressure changes during maximum treadmill exercise

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Data from maximum exercise tests undertaken by 4714 men enrolled in a prospective epidemiological study has been analysed to determine the significance of systolic pressure changes. The average change in 2532 healthy men was 61±19 mmHg and in 1586 men with clinical coronary artery disease was 37±27 mmHg ($P<0{\cdot}001$). Among the 1586 with coronary artery disease followed for an average period of 22±9 months, there were 96 deaths caused by coronary artery disease. The risk of coronary artery disease death was greatest in those men with small increases in systolic pressure. Dividing the total group into quartiles according to change in systolic pressure (ΔSBP) a gradient of risk was shown. The mortality rate for those with ΔSBP less than 19 mmHg was 86 per 1000 men per year and for those with ΔSBP above 56 mmHg was 4 per 1000 men per year ($P<0{\cdot}05$). Men with coronary artery disease whose systolic pressure increased by more than 61 mmHg (i.e. average for healthy men) had no subsequent mortality.

In contrast, ischaemic ST depression during or after exercise was not a significant predictor of subsequent coronary artery disease mortality. The mortality rate for men with horizontal ST depression (1 mm or more) was 44 per 1000 men per year and for those without such changes, 33 per 1000 men per year.

Five episodes of post-exertional ventricular fibrillation developed in 8640 tests. All were in individuals whose systolic pressure failed to increase with exercise.

Systolic pressure changes during exercise testing are helpful in assessing prognosis and have practical importance for the safety of exercise tests in men with coronary artery disease.

Electrocardiographic changes resembling myocardial ischaemia in asymptomatic men with normal coronary arteriogram

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ST and T abnormalities in 20 asymptomatic men aged 18 to 55 were investigated because they were identical with myocardial ischaemic changes. Characteristically the changes were temporarily suppressed by either beta-blockade, an overnight rest, or hyperventilation; they were more abnormal in the standing position. Maximal treadmill exercise tests were positive (greater than 1 mm ST depression) in 6 and borderline or negative in 14. When repeated after oxprenolol all were negative. After normalisation by an overnight rest the T abnormalities were reproduced by intravenous adrenaline infusion (0·024 to 0·091 μg/kg per min) but not by noradrenaline, atrial pacing, or after prior administration of oxprenolol. When the T waves were spontaneously abnormally flat or inverted, adrenaline infusion normalised them and noradrenaline was without effect. Plasma catecholamine concentrations monitored during exercise, beta-blockade, pacing, and catecholamine infusion studies suggest that catecholamine hypersecretion and hypersensitivity may be relevant. The apparent bimodal repolarisation of the ventricular myocardium to adrenaline infusion is not surprising since *in vitro* experiments suggest that similar T changes can result from action potential changes of opposing direction in different parts of the heart.

Six-month to 5-year follow-up of 343 aortocoronary bypass operations

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From 1971 to 1976, 343 of 893 patients investigated for coronary disease underwent bypass grafting: 304 were men and 39 women. The median age was 50. Twenty per cent had single, 44 per cent double, 30·5 per cent triple and 5·5 per cent quadruple grafts. In addition endarterectomy was performed in 68 patients, aneurysmectomy in 18, closure of ventricular septal defect in 6 and mitral annuloplasty in 5. The hospital mortality was 5 per cent (3·7% for vein graft procedures only). Follow-up was 6 to 60 months (average 23·7). 10·6 per cent of patients had a postoperative (Q wave) myocardial infarction (5·9% perioperative, 4·7% late). There were 11 late deaths (overall mortality 8·2%). Seventy-five per cent of deaths occurred within 6 months of surgery. At 3 years 90·4 per cent were surviving. The survival of the medically treated group (445 patients) was not significantly different at that stage.

80·2 per cent of the patients are asymptomatic, 5·5 per cent improved (>2 grades), 10·5 per cent unchanged, 1 per cent worse, and 2·8 per cent lost to follow-up. Angina grade preoperatively was 2·48 compared with 0·32 at the latest follow-up ($P=0·001$), and maximum exercise load was also significantly improved ($P=0·001$) ($n=277$). The excellent clinical result of aortocoronary bypass is maintained over a period of up to 5 years; late morbidity and mortality appears to be similar to that of medically treated patients.

Left main coronary artery obstruction: experience of 41 patients

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Between June 1972 and August 1975, 1300 patients underwent coronary arteriography at Harefield Hospital for the investigation of suspected coronary artery disease. Forty-one patients (3·2%) were found to have 70 per cent or more obstruction to the left main coronary artery and form the subject of this communication. There were 39 men and 2 women, with a mean age of 56 years. All patients were symptomatic and 33 (80%) were in functional Class 3 or 4 using the New York Heart Association classification. Sixteen patients (38%) experienced unstable angina. In 35 patients (85%) the resting electrocardiogram was abnormal and showed previous myocardial infarction in 21 patients (51%). Coronary arteriography was performed in all patients, using the Judkins technique, and there were no major arrhythmias or deaths associated with this procedure. The striking finding at coronary arteriography was the presence of significant disease in other major coronary vessels. The left ventriculogram showed abnormalities in the contraction pattern in 31 (78%) of 40 patients. Twenty-nine patients underwent saphenous vein aortocoronary bypass grafting with additional aortic valve replacement in 2 patients for severe aortic stenosis. There were 2 early deaths (6·9%) and 1 late death (3·4%). Of these 3 patients, 2 had poor preoperative left ventricular function. Twelve patients did not undergo surgery. Of these, 2 died while awaiting operation, 1 refused operation, and the remainder were unsuitable for surgery as a result of extremely poor and diffuse left ventricular dysfunction. Twenty-one patients have been followed up from between 3 and 30 months (mean 16·4 months). All patients are improved, and 17 (81%) are completely symptom free. Twenty-one (75%) of the 29 patients treated surgically underwent repeat coronary, graft, and left ventriculography at a mean period of 9·8 months after operation. The overall graft patency rate was 91 per cent. Postoperative left ventricular function as assessed by angiocardiography and measurement of ejection fraction shows significant improvement in the majority of patients.

Contribution of resting electrocardiograph to air transport safety

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Professional aircrew and Air Traffic Control Officers (ATCO's) are required to undergo routine medical examination and electrocardiography at intervals which are related to their age. Scrutiny was made of 5217 resting electrocardiograms representing a population sample of approximately 8840 between September 1974 and December 1975. The recordings were made by 80 different examiners on 20 different models of recording apparatus.

A wide range of possible electrocardiographic abnormalities was recorded for 365 aircrew. The most frequent were abnormalities of the ST segment, the J point, or the T wave in the anterolateral leads (65) or the inferior leads (85). Stable left axis deviation was also frequent (90) as were non-diagnostic Q waves (20). Conduction defects were uncommon and pre-excitation syndromes rare. Eight-four aircrew or ATCO's were recommended for referral for further cardiological assessment and as a result, 13 were classified permanently unfit. During the period under review, 6 pilots lost their licences because of ischaemic heart disease first presenting as myocardial infarction (5) or angina (1). Four of these were under surveillance for hypertension, diabetes, or intermittent claudication.

These findings were discussed in relation to problems of interpretation of the resting electrocardiogram and the licensing of pilots. The usefulness of the exercise electrocardiogram in this context was also discussed.

Role of ambulatory electrocardiographic monitoring; accuracy of quantitative analysis system

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Twenty-four hour ambulatory electrocardiograms have been recorded in over 400 patients. Accurate diagnosis has been obtained in cases of: (a) symptomatic tachyarrhythmia; (b) unexplained syncope or apparent epilepsy; (c) episodic conduction disturbance. In addition, quantitative assessment of antiarrhythmic drug efficacy has recently become possible.

The Reynolds Pathfinder rapid analyser (Neilson) has been assessed in 25 patients with disabling ventricular arrhythmias. All subjects had frequent ventricular premature beats (VPBs) (Grade 2, Lown and Wolf, 1971). VPBs in couplets or ventricular tachycardia (Grades 4a and b) were present in 19 of the 25.

Entire 24-hour tapes were transferred to paper at a speed of 10 mm/s. Over 337 000 VPBs were hand counted and assigned to their Lown grades. These tapes were independently analysed on the Pathfinder at 60 × real speed. Correlation for all arrhythmia grades was extremely close ($r=0{\cdot}89$ for VPBs, 0·95 for couplets, and 0·98 for ventricular tachycardia). The controlled oral efficacy of mexiletine was investigated using this system. Grade 2 VPBs were reduced by over 75 per cent in 13 of the 25 patients. Grade 4a and 4b arrhythmias were reduced by over 95 per cent in 11 of 19 and 7 of 14 cases, respectively.

It is concluded that the Pathfinder represents a major advance over other available commercial equipment in qualitative and quantitative assessment of ventricular arrhythmias.

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Surface recording of electrical activity in the PR segment in man

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A method has been developed for the non-invasive recording of electrical activity in the PR segment in man. Signals from chest surface electrodes are amplified 0·5 to $2{\cdot}0 \times 10^6$ times and filtered to select frequencies between 40 and 500 Hz. Noise in the resulting signal is reduced using computerised digital averaging of between 150 and 500 cycles. A time reference point required for averaging is derived from a change in slope of the QRS complex of a separate surface electrocardiogram. Digital filtering is used to eliminate high frequency residual noise after averaging.

The system has been shown to recover the surface deflection resulting from an implanted His pacing stimulus of only 20 mV.

Highly repeatable electrical deflections were recorded in the PR segment in 2 healthy male subjects on whom the method was initially developed. Nine of 11 similar subjects subsequently examined showed recognisable patterns of activity within the PR segment.

External recordings have been made in 10 patients undergoing simultaneous conventional His bundle electrocardiography for conducting system disease. In 8, surface deflections have been obtained synchronous with the internal His waveform. In 6 cases the configuration of internal and external signals was identical. We believe this technique to be worthy of further development.

Assessment of drug effect in pre-excitation syndrome

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The purpose of this study was to evaluate electrophysiological measurements in assessing the effect of antiarrhythmic therapy in the pre-excitation syndrome. The most useful index was found to be the shortest RR interval in milliseconds between consecutive pre-excited QRS complexes during electively induced atrial fibrillation (SRRIAF). This could be measured in 32 of 33 untreated patients with pre-excitation syndrome. It was found to correlate well with the patients' preadmission history. Of the 22 patients whose SRRIAF was <205 ms, ventricular fibrillation had occurred in 10 and 8 had had tachycardias of 300+/min. These arrhythmias were not documented in any patients whose SRRIAF >210 ms. Twenty-eight patients received 10 mg/kg IV procainamide and in 21 atrial fibrillation could be induced. The SRRIAF increased by 20 to 70 ms in 15 and was unchanged in 6. Twenty-three patients received oral quinidine (200 to 400 mg 6 hourly for 2 to 4 days) and in 16 atrial fibrillation could be induced. The SRRIAF increased in all by 20 to 170 ms.

We conclude that the measurement of SRRIAF is of value in predicting the probable clinical usefulness of specific antiarrhythmic drugs in individual patients with pre-excitation syndrome.

Dual demand pacing for refractory re-entry atrioventricular tachycardias

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Refractory atrioventricular (AV) re-entry tachycardias may be controlled by a pacemaker which interrupts attacks with fixed-rate 'underdrive' pacing. This alternative means of treatment has been studied in 36 patients with such arrhythmias, during intracardiac electrophysiological studies; 28 had the WPW syndrome, 8 had intra-AV nodal re-entry. Successful underdrive pacing from one or more sites could be predicted if tachycardias were stopped by *single*, suitably timed premature beats; such sites were found in all cases with WPW syndrome, but in only 3 with intra-AV nodal tachycardia.

Underdrive pacing was most rapidly effective (less than 30 seconds) if the tachycardia was relatively slow; if there was a pronounced discrepancy between the effective refractory periods of the myocardium being stimulated and of that part of the circuit where tachycardia was most easily blocked; and if the conduction time from the electrode to this site was short. In pre-excitation the electrode should be positioned on the same side as the accessory pathway. Use of appropriate antiarrhythmic drugs in addition enhanced the effectiveness of this form of treatment in both types of AV re-entry tachycardia.

Dual demand self-activating pacemakers have been implanted successfully in 4 such patients with otherwise refractory AV tachycardias.

Paroxysmal re-entrant AV nodal tachycardia with 2:1 block

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It is widely held that a supraventricular tachycardia originating within the AV node could not be a re-entrant tachycardia if anterograde AV block was present. A group of patients with paroxysmal nodal tachycardia and anterograde block are presented. In 2 patients the level of block was infra-Hisian. In one patient anterograde block was supra-Hisian and in this same patient retrograde block occurred.

Tachycardias with 2:1 block were initiated by atrial premature beats. Ventricular premature beats (VPB) only initiated tachycardias with 1:1 conduction. In all instances 2:1 tachycardia was converted to 1:1 conduction by an appropriately timed VPB and in 2 cases right bundle-branch block in 1:1 tachycardia was converted to normal conduction by an appropriately timed VPB.

The tachycardias were not terminated by a single VPB and coupled VPBs produced in 2 patients transient disorganised ventricular activity. Underdrive ventricular pacing would not terminate these tachycardias but converted 2:1 tachycardia to 1:1 conduction with symptomatic deterioration. Rapid atrial stimulation or coupled atrial premature beats terminated both forms of tachycardia. In 2 cases long-term treatment (6 months and 3 years) with patient controlled, high frequency, atrial pacemaker systems has been uniformly successful.

Disopyramide in the sick sinus syndrome—safe or not?

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Disopyramide is of value in the management of arrhythmias and it is reported that it can be used safely in arrhythmias associated with the sick sinus syndrome.

Nine patients, 6 with sick sinus syndrome, were studied before and 15 minutes after the onset of infusion with disopyramide 2 mg/kg over 15 minutes and 2 mg/kg over the next 45 minutes. In addition 1 of the 6 with sick sinus syndrome was studied on oral disopyramide.

Sinoatrial node function was assessed by: 1 spontaneous cycle length (A_1A_1), (2) maximal sinus recovery time obtained from repeated atrial pacing at various cycle lengths and (3) sinoatrial conduction time estimated using premature atrial stimulation.

At least one of the above was abnormal in the 6 patients with sick sinus syndrome before disopyramide. Deterioration in sinoatrial node function occurred during disopyramide in all 6.

Sinoatrial block developed or increased in 4/6, maximal sinus recovery time increased in 4/6, and sinoatrial conduction time lengthened in 1/2 in which it could be measured before and after disopyramide.

The three patients without sick sinus syndrome showed no significant change in A_1A_1 (1030 ± 232 to 936 ± 162), maximal sinus recovery time (1352 ± 154 to 1365 ± 357) or sinoatrial conduction time (93 ± 19 to 92 ± 10).

In conclusion disopyramide may result in deterioration in sinoatrial node function in patients with sick sinus syndrome and may dangerously prolong post-tachycardia pauses.

Clinical cardiovascular pharmacology of unique inotropic agent, UK 14275; a phosphodiesterase inhibitor

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An orally active inotropic agent which lacks significant chronotropic effects would be of major value in the management of impaired left ventricular function, however caused. UK 14275, a phosphodiesterase inhibitor, is unique in possessing these properties in experimental animals.

The inotropic effect of intravenous UK 14275 in concentrations of 64 and 128 μg/kg bodyweight per min on systolic time intervals was observed in 7 volunteers. Pre-ejection period (PEP) and PEP/LV ejection time were reduced by 22 ± 4 per cent (19 ± 6 ms) and 20 ± 5 per cent, respectively, at a concentration of 128 μg/kg per min. No chronotropic effects were observed. Beta blockade with oral propranolol abolished these changes.

The haemodynamic effects of intravenous UK 14275 were measured directly in 7 patients undergoing diagnostic catheterisation because of suspected coronary artery disease. In concentrations of 128 and 256 μg/kg per min, UK 14275 produced no chronotropic changes. Cardiac output increased from 3·3 to 4 l/min ($P < 0·02$), LV dp/dt max. increased from 1332 to 2004 mmHg/s (43%, $P < 0·05$). LV end-diastolic pressure fell from 12·5 to 10 mmHg ($P < 0·05$). There were no changes in systolic or mean arterial pressure.

UK 14275, therefore, has significant inotropic activity. It is chemically and pharmacologically unique and being active both orally and parenterally is of great potential therapeutic valve.

Endomyocardial biopsies: is pathological examination of use?

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Reports as to the value of morphological analysis of fresh endomyocardial biopsies obtained by the bioptome techniques are controversial.

In this paper, material obtained from over 350 patients (average number of biopsies 3·8 per patient) received from various London centres, and from abroad, was presented. The right ventricle was sampled in all but 10 patients (these 10 underwent left ventricular biopsies alone). In 42 patients, right and left ventricular samples were obtained simultaneously. Approximately two-thirds of patients were suspected to suffer from cardiomyopathy, the remainder from other entities, including myocarditis and amyloid.

Histological and ultrastructural changes were briefly illustrated, and reference to histochemical analysis was made.

The results show that helpful information can be obtained in 70 per cent of patients.

Evidence from subsequent necropsy of 9 hearts lends support to the view that the small samples obtained reflect the state of the rest of the myocardium fairly accurately if the underlying disease process is widespread, or where the lesion can be located.

It is concluded that pathological examination can be a useful adjunct to diagnosis in carefully selected patients. Furthermore, it forms an essential reference point for other investigations, such as biochemistry.

Negative feedback process for regulation of cardiac action potential duration

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In calf and sheep ventricular fibres inactivation of inward calcium current against a background outward current causes repolarisation. Thus, the level of the outward current will affect the action potential duration. In several cell types a relation between intracellular calcium concentration $[Ca]_i$, and potassium permeability, pK, manifested by an outward current, has been proposed and such a possibility was investigated here with the voltage-clamp technique.

$[Ca]_i$ was increased by raising the stimulation frequency or reducing $[Na^+]_o$, with the addition of external CN^-, both procedures causing an increase in outward current. The frequency-dependent increase was partially blocked by the calcium current inhibitors D600 and verapamil.

As expected, decrease in stimulation frequency led to an increase in action potential duration, but at very low stimulation frequencies the duration was again shortened. Replacement of external Cl^- by the impermeable anion isethionate prevented such a shortening.

We suggest that a feedback process exists between $[Ca]_i$ and pK controlling the action potential duration. Cl^- ions produce an additional stabilising effect, only becoming manifest at very low stimulation frequencies.

Comparison of arrhythmogenic potential of mianserin, amitriptyline, and maprotiline with reference to noradrenaline uptake in isolated perfused rabbit hearts

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In isolated perfused rabbit hearts, (-)-noradrenaline (0·0059 to 5·9 μmol) increased frequency and force of contractions and shortened the time between peak atrial and ventricular tension development (AV contraction interval) but no arrhythmias were observed. Inclusion of amitriptyline or maprotiline (4·8 μmol) in the perfusion fluid altered the response to noradrenaline such that the AV contraction interval was lengthened and arrhythmias developed. Mianserin (4·8 μmol) did not alter the response to noradrenaline but at 28·8 μmol some hearts became arrhythmic. The arrhythmias resembled those produced by higher concentrations of antidepressant drugs in the absence of noradrenaline (i.e. predominance of AV block). The uptake of ^{3}H-(-) noradrenaline was completely blocked by all three drugs at 4·8 μmol. A relation between inhibition of noradrenaline uptake and predisposition to noradrenaline-induced arrhythmias in the presence of antidepressant drugs is placed in doubt.

Actions of cardiac glycosides and diuretics on Na-pump activity and Na-permeability in frog ventricle fibres

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Using frog ventricle, we investigated actions of cardiac glycosides (cg), ouabain (o), and digoxin (d); and diuretics ethacrynic acid (ea), bumetanide (b), amiloride (a), and SC14266 (c) on

(1) Na-permeability appraised during net Na-accumulation from cold (0°C) K-free Conway-Ringer (C-R: 120/0 mM·l^{-1} Na/K)
(2) Na pump activity in Na-enriched fibres (by prior immersion as in (1)) during net extrusion in oxygenated C-R (120/10).

In each experiment ventricles from 10 frogs were halved and weighed, the left halves being immersed with, the right without, additive. After immersion, hemiventricles were analysed for H_2O, K, Na, Cl, and extracellular fluid volume and cell composition determined. Methods are described elsewhere (Flear *et al.*, 1976a, b). Control experiments established identity of compositions of left and right pairs—unimmersed, Na-enriched, and after Na-extrusion. Experiments with additives established *pump activity stimulated and permeability decreased* by o ($<10^{-7}$M), ea (10^{-7} and 10^{-5}M, respectively), a (10^{-5} and 10^{-3}M, respectively), *pump inhibited, permeability increased* by c ($>10^{-4}$ and 10^{-7}M respectively), ea (10^{-3}M); d: pump stimulated ($<10^{-7}$M), inhibited ($>10^{-6}$M), permeability not investigated; b: pump, no effect; permeability decreased (10^{-7}M); c: pump impaired (10^{-3}M), permeability unaffected; 10^{-3}M c reduces pump-inhibition and permeability increase by o, but does not oppose pump-stimulation, and increases permeability reduction by o.

Results compel reappraisal of the view that cardiac glycosides strengthen contraction by inhibiting Na-pump activity: and consideration of effects of diuretics on heart and action of cardiac glycosides.

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Action of caffeine upon calcium accumulation by sarcoplasmic reticulum preparations isolated from rabbit heart

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Caffeine partly influences mechanical performance of heart muscle by affecting internal membrane function. In skeletal and heart muscle caffeine alters calcium accumulation by isolated sarcoplasmic reticulum fractions but the manner of its action is uncertain. Sarcoplasmic reticulum fractions were isolated from rabbit heart by differential centrifugation. Calcium accumulation, with and without oxalate, was followed using dual-wavelength spectrophotometry with murexide at 35°C. The calcium accumulation data were analysed according to first order kinetics. ATPase activity (basic and calcium activated) was also measured. Calcium accumulation both with and without oxalate was inhibited in a dose related manner by caffeine. At low but not high concentrations calcium activated ATPase activity was increased by caffeine but in the presence of oxalate it was not altered by caffeine at any calcium concentration. Caffeine did not alter the basic ATPase activity. The findings support the conclusion that caffeine reduced calcium accumulation by altering the passive permeability of the sarcoplasmic recticulum vesicles to calcium.

Pharmacological protection of hypoxic heart[1]

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When perfused under hypoxic conditions isolated heart muscle fails; developed tension decreases and end-diastolic resting tension increases. These changes in mechanical function are accompanied by ultrastructural damage that involves the plasmalemma, the mitochondria, and the myofilaments. The tissue gains Na$^+$ and Ca^{2+}, and loses K$^+$. After relatively long periods of hypoxia the Ca^{2+}-accumulating activity of the sarcoplasmic reticulum decreases. After relatively short periods of hypoxia the Ca^{2+}-accumulating activity of the mitochondria increases and their P/O ratio declines. *dl* verapamil and *dl* propranolol protect the mitochondria against these effects of hypoxia. They also prevent the hypoxic muscle from developing a raised end-diastolic resting tension. These results have been interpreted to mean that the increase in end-diastolic resting tension that occurs when heart muscle is made hypoxic may involve a reduction in the ability of the mitochondria to synthesise APT consequent upon Ca^{2+}-overload.

Hypothermic and metabolic protection of myocardium in cardiac bypass and arrest

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The protection of the ischaemic myocardium during heart surgery with cardiopulmonary bypass and cardiac arrest can be resolved into two components. Firstly, the use of cardioplegic agents for the rapid induction of arrest, the prevention of ischaemic beating and the consequent conservation of cellular energy, and, secondly, the use of metabolic protective agents to combat the deleterious cellular changes which occur as a result of tissue ischaemia. Using an isolated working rat heart model we have investigated, both individually and in combination, the effect of a number of cardioplegic and metabolic protective agents (potassium, magnesium, procaine, glucose, insulin, mannitol, ATP, creatine phosphate, acetyl choline, adenosine, aspartate, methyl prednisolone, hydrocortisone, and topical hypothermia) upon the recovery of heart from periods of bypass and ischaemia. The effect of these agents on cellular energy metabolism has also been investigated in studies in which myocardial adenosine triphosphate and creatine phosphate have been measured during ischaemia. Multicomponent solutions have been formulated which, if infused into the heart for 2 minutes before the onset of ischaemia, permit hearts which would fail to recover from 30 minutes normothermic ischaemia, to recover almost 100 per cent of their cardiac output after 60 minutes of ischaemia. Dose response studies have been carried out for selected components and the recoveries of the hearts have been related to the duration of ischaemia and to the degree of topical hypothermia maintained during ischaemia.

Effect of glucose on ventricular vulnerability in acute myocardial ischaemia

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The vulnerability of the myocardium to the development of ventricular premature beats (VPB) may be tested by the method of sequential R/T pulsing. Three consecutive suprathreshold stimuli are applied each on the 'vulnerable period' of the preceding beat. By increasing the strength of the third pulse, multiple VPB, and finally ventricular fibrillation can be induced.

VPB thresholds (VPBT) have thus been determined in dogs during and after repeated 10-minute occlusions of the anterior descending coronary artery. Sharp reductions in VPBT occurred between 3 and 6 minutes after occlusion and in some dogs immediately after release.

During glucose infusion (17·5 mg/kg per min), producing a significant rise of blood glucose. the expected fall in VPBT was delayed and reduced 5 minutes after occlusion ($P < 0{\cdot}05$). There was no significant difference after 10 minutes. No such difference was seen after iso-osmolar infusions of mannitol.

Sequential blood sampling was performed from the femoral artery and the local coronary vein draining the ischaemic area. Preliminary data reveal an increase arterial local vein difference in glucose during glucose infusions.

It is concluded that increased availability of glucose to the ischaemic myocardium temporarily reduces its vulnerability to the development of lethal arrhythmias.

Lysosomal enzyme release in acute myocardial infarction[2]

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Lysosome disruption and release of N-acetyl-β-glucosaminidase has been shown to occur at the onset of cell death in experimental myocardial anoxia (Welman and Peters, 1976). Analytical subcellular fractionation of human myocardium showed that this enzyme was localised to the major population of lysosomes in this tissue. Consequently, studies were carried out in patients with acute myocardial infarction to determine whether plasma N-acetyl-β-glucosaminidase activity was raised. In 35 patients with clinical, electrocardiographic, and enzyme evidence of infarction an increase in plasma N-acetyl-β-glucosaminidase activity was found between 6 and 24 hours after the onset of chest pain. In uncomplicated cases the peak level occurred at 18 hours. There was a close relation between the peak values of the lysosomal enzyme and those of creatine phosphokinase and its cardiac-specific isoenzyme. These findings support the suggestion that lysosome disruption is involved in ischaemic myocardial necrosis and show that lysosomal changes can be studied by serial measurements of the activity of this marker enzyme in the plasma.

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[2] This work was supported by the British Heart Foundation and the Medical Research Council.

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Subcellular compartmentation of creatine kinase isoenzymes in guinea pig heart

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In an attempt to determine whether a subcellular compartmentation of creatine kinase (CK) exists and if so, whether there is a differential distribution of the isoenzymes of CK in cardiac cells, studies were carried out with the guinea pig heart which had been subfractionated into myofibrils, mitochondria, microsomes, plasma membrane, and cytosol by either isopycnic centrifugation or differential pelleting. Analysis of total CK in the isolated subcellular fractions revealed mainly a cytosolic localisation with smaller amounts of activity in the mitochondria, the myofibrils, and the microsomes. No CK activity was associated with the plasma membrane.

Isoenzyme analysis of CK in these fractions revealed that the MM isoenzyme occurred in the cytosol, the myofibrils, and the microsomes while the cardiospecific MB isoenzyme together with trace amounts of the BB isoenzyme occurred only in the cytosol, CK activity in the mitochondria did not represent either of the MM, MB, or BB isoenzymes but was a distinct and additional mitochondrial specific form of the enzyme. Studies were carried out to compare the *p*H optima and kinetics of the mitochondrial isoenzyme with the cytosolic isoenzymes. The evidence for a differential compartmentation of M, MB, BB, and mitochondrial CK was discussed in relation to their possible cellular roles.

Local infusion of ATP, creatine phosphate, or methylprednisolone, in acute myocardial infarction

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The acutely ischaemic myocardium rapidly depletes its endogenous reserves of adenosine triphosphate (ATP) and creatine phosphate (CP). It releases inorganic phosphate and potassium with the activation of anaerobic glycolysis, inhibition of oxidative phosphorylation, and inactivation of sodium/potassium pump. At a later stage of ischaemia, intracellular enzymes are released. These biochemical changes are accompanied by structural changes; and the initially reversible injury becomes irreversible when the processes of energy production can no longer maintain cellular integrity.

The effect of an artificial increase of local levels of ATP, CP, and the infusion of methylprednisolone into an area of acutely ischaemic myocardium has been studied in 36 rabbits *in vivo*. Changes in the plasma levels of cardiac enzymes, potassium, and inorganic phosphate have been measured along with the rise in the artificial pacing threshold in μJ during the first 6 hours after coronary ligation. The ultrastructure has been studied in biopsies from the ischaemic area.

Significantly improved levels were found in CK ($P<0{\cdot}001$); LDH ($P<0{\cdot}05$); SGOT ($P<0{\cdot}001$); K^+ ($P<0{\cdot}05$); inorganic phosphate ($P<0{\cdot}001$) and the pacing threshold ($P<0{\cdot}001$) at 6 hours after coronary occlusion in those animals where ATP was infused locally.

Creatine phosphate infusion also offered significant improvement 1 to 4 hours post-coronary ligation.

Release of CK ($P<0{\cdot}001$), K^+ ($P<0{\cdot}05$) and inorganic phosphate ($P<0{\cdot}005$) were also significantly reduced with the infusion of methylprednisolone.

The study has shown that an increase in local levels of ATP offers better protection of the ischaemic myocardium than creatine phosphate and methylprednisolone.

Demonstration of pulmonary arteries by contrast injection into a pulmonary vein

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The anatomical characteristics of the pulmonary arteries were investigated in 10 patients with pulmonary atresia or underdeveloped pulmonary arteries, by selective pulmonary venous angiography and by conventional cardiac catheterisation and angiography. By injecting radio-opaque contrast medium into a pulmonary vein it was possible to show the size and extent of the pulmonary arteries much more clearly than by standard methods. The passage of contrast medium to the pulmonary arteries appeared to take place through proximal communicating channels, and not via pulmonary capillaries. Opacification was early and dense. There has been no short-term patient morbidity from this investigation and follow-up chest radiographs have shown no new changes.

Intra-atrial activation mapping during Mustard operation for transposition of great arteries

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Thirty-two patients with transposition of the great arteries (TGA) underwent epicardial and endocardial atrial mapping during different stages of the Mustard operation. The zones of preferential conduction between the sinus node and the atrioventricular node (AV node) can be altered at all stages. The cannulation site of the superior vena cava does not seem to alter the intra-atrial conduction. A transverse atriotomy across the sulcus terminalis interrupts the posterior input to the AV node, whereas a longitudinal atriotomy, anterior to the sulcus terminalis, does not create any delay of activation of the AV node. The excision of the interatrial septum does not change significantly the intra-atrial activation. If the coronary sinus is cut back (11 patients), the terminal portion of the posterior input to the AV node is interrupted. The practical significance of these alterations of the intra-atrial conduction was investigated with the 24-hour electrocardiogram monitoring after Mustard operations.

Late results of Mustard's operation for transposition of great arteries

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This investigation was undertaken to demonstrate the quality of life up to nine years after Mustard's operation for transposition of the great arteries (TGA). In 1975, assessment was made in 164 survivors of Mustard's operation between 1965 and 1971. Attention was focused on the life style and physical achievements of the survivors. Fifty-six of the survivors attend normal schools and participate in sporting activities. A further 46 lead unrestricted lives, but with some complication (e.g. arrhythmia or tricuspid regurgitation). Twenty-one patients were restricted by a severe arrhythmia. Severe neurological deficits were present in 7 survivors. It was not possible to assess the 9 patients living abroad, though they are known to be alive. There were 36 deaths, occurring 2 months to 6 years postoperatively. Main or contributory causes of death were: patch obstruction in 10, arrhythmias in 12, and tricuspid regurgitation in 4 cases. Arrhythmias were the main cause of disability and contributed significantly to the mortality. Right ventricular and tricuspid valve function were not found to be factors limiting a good functional result.

Clinical and haemodynamic results of primary total correction of Fallot's tetralogy in first two years of life

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Twenty-five children who underwent successful primary total correction of tetralogy of Fallot under the age of 2 years have been followed up for a minimum period of 1 year (mean 31 months). Homograft reconstruction of the right ventricular outflow tract (RVOT) was performed in 9. All children are asymptomatic and growing normally. Five children had no murmurs. The remaining children have varying degrees of pulmonary ejection murmurs. Radiologically the heart size was within normal limits. The children with reconstruction of the RVOT all have linear calcification in the wall of the homograft. Twenty-one have been reinvestigated at periods of up to 3 years postoperatively. The peak RV: LV ratio was between 0·2 to 0·4 in all except 1 patient who developed an aneurysm of the RVOT. There was no evidence of re-opening or residual ventricular septal defect. Angiography showed good development of the RVOT in all except the patient with the aneurysm. It is concluded that normal physical development, growth of the RVOT with no evidence of restenosis or reopening of the ventricular septal defect continues up to 4½ years after primary total correction below the age of 2 years.

Left heart lesions presenting with Eisenmenger complex

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Seven patients aged 4 to 11 years with pulmonary hypertension, a right-to-left shunt through a persistent ductus arteriosus or ventricular septal defect (the Eisenmenger complex) and serious left heart lesions have had surgical treatment.

Mitral stenosis was present in 3; mitral regurgitation in 2, a supravalvar membrane in 1, and aortic valve stenosis with cardiomyopathy in 1; an associated coarctation was present in 3. All patients presented with the features of severe pulmonary hypertension, confirmed by cardiac catheterisation, and the important left heart lesion was usually missed. However, there were always clinical or radiological signs suggesting the presence of aortic or mitral valve disease; echocardiography confirmed the left atrial obstructive lesion in 4.

Six patients had valve replacement or repair, in 1 the supravalve membrane was resected, and in 3 the coarctation was resected. After this, closure of the duct or ventricular septal defect, with a fall in the pulmonary artery pressure, was possible in 6 of the 7.

Diagnosis of the masked left heart lesion is vital in this group of patients who are frequently and erroneously deemed inoperable.

Surgical correction of coarctation of aorta in infancy (4 days to 6½ months) using left subclavian artery flap aortoplasty

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This technique has been developed since 1969 in an attempt to lower the high natural mortality of this condition and its frequently associated lesions (viz. ventricular septal defect and persistent ductus arteriosus) in infancy and to reduce the incidence of 'restenosis'.

Plastic enlargement of the narrowed aorta is performed using the open out left subclavian artery as a pedicled flap. This allows growth in girth at the site of coarctation *pari passu* with the child's development.

Pulmonary artery banding is performed when indicated and the persistent ductus arteriosus is ligated or divided.

Thirty-nine infants aged 4 days to 6½ months form the basis of this report. Cine aortography and haemodynamic pressure studies up to 6 years postoperatively show that the reconstructed aorta has grown satisfactorily.

Only 2 of 23 surviving children have 'unsatisfactory' femoral pulsations.

Thirty infants were under 3 months of age at the time of surgery (mortality 43%).

The overall hospital mortality is 33%. A detailed analysis of the results and follow-up studies was presented.

Echocardiographic assessment of left ventricular filling after mitral valve surgery

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In order to investigate the functional effects of mitral valve surgery, echocardiograms showing left ventricular (LV) dimension were recorded and digitised in 10 normal subjects and 111 patients after mitral valve surgery. Measurements were made of peak rate of increase of dimension (dD/dt) and duration of rapid filling, studies on left ventriculograms having shown close correlation between these values and changes in cavity volume. In 11 patients with mitral stenosis, peak dD/dt was reduced to 7·3 ±1·5 cm/s, and filling period prolonged to 330 ±65 ms, compared with normal (15·6 ±6 cm/s, and 160 ±50 ms, respectively, $P < 0{\cdot}01$), and after mitral valvotomy, these values improved significantly (10·5 ±2·7 cm/s and 250 ±55 ms, $P < 0{\cdot}01$). Characteristic abnormalities were found in 70 patients with mitral prostheses. Values for the Bjork-Shiley (10·5 ±4·2 cm/s and 180 ±80 ms) and Hancock (10·3 ± 3·7 cm/s, 200 ±85 ms) valves were similar, and both superior to the Starr-Edwards (7·4 ±3 cm/s, 300 ±105 ms, $P < 0{\cdot}01$). Results after mitral valve repair in 30 cases were not significantly different form normal (14 ±5 cm/s, 170 ±50 ms). Values outside the 95 per cent confidence limits for the valve in question allowed diagnosis of valve malfunction in 20 cases. In summary, this method can be used to compare surgical procedures and to follow up patients after mitral valve surgery.

Combined homograft replacement of aortic valve and aortic root with reimplantation of coronary arteries

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Between December 1975 and May 1976, 16 patients underwent homograft replacement of the aortic valve combined with aortic root replacement and reimplantation of the coronary arteries into the homograft. Early results show that this technique allows the use of a larger homograft in children and in the adult patients with a small aortic root. It permits complete anatomical reconstruction of the ascending aorta in patients with aneurysms or other lesions involving the aortic root, and prevents any distortion of the homograft valve. There were 7 male and 9 female patients aged between 10 years and 58 years (mean 32). The aetiology of the valve lesions was Marfan's syndrome in 3 cases, dissecting aneurysm resulting from medial necrosis in 2, infective endocarditis in 4, rheumatic or congenital valve disease in 5, prolapsed aortic cusp with ventricular septal defect in 1, and non-specific aortitis in 1. The haemodynamic lesion was aortic regurgitation in 13 cases and aortic stenosis in 3. There have been no early or late deaths and all patients are improved (follow-up 1 to 5 months). Cardiac catheterisation and aortography in 6 patients has shown the homograft valve to be competent in each case, with normal coronary filling.

Angina in aortic stenosis and its relation to coronary artery disease and results of homograft replacement of aortic valve

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Between 1969 and 1975, 80 patients with aortic stenosis and angina were investigated by coronary angiography (CA) and cardiac catheterisation before aortic valve replacement (AVR) in an attempt to define more precisely the aetiology of their angina. There were 59 men and 21 women aged between 30 and 71 years (mean 58). CA was normal in 56 patients (70%), 8 (10%) had single vessel disease, 9 (11%) had double vessel disease, and 7 (9%) had triple vessel disease. Age of onset, severity and duration of symptoms, electrocardiogram, and haemodynamic parameters were not related to coronary artery disease (CAD) or its severity. Isolated AVR was performed in 64 patients with additional coronary artery bypass grafting (CABG) in 16. There were 2 early deaths (2·5%) and 2 late deaths (2·5%) with a follow-up of 3 to 72 months (mean 20). Twenty-seven patients underwent reinvestigation at a mean time of 23 months after AVR. Left ventricular function improved in most patients irrespective of CAD or CABG, but abnormalities of segmental wall motion, present only in the CAD group, did not improve despite CABG. It is concluded that the presence of CAD in aortic stenosis cannot be predicted without CA. Left ventricular function improves after AVR despite CAD but in the short term CABG does not appear to produce additional improvement.

YOUNG RESEARCH WORKERS' PRIZE

Dependence of myocardial blood flow and metabolism on cardiac innervation

Angela J. Drake
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Sussex

Left ventricular blood flow was measured in dogs with ^{141}Ce-labelled microspheres at a fixed heart rate for each dog, achieved by right atrial pacing. Blood samples were taken from an artery and from the coronary sinus, into which a catheter had been introduced under fluoroscopic control. These were analysed for oxygen content, lactate, glucose, and free fatty acids (FFA). The coronary AV differences for these variables were used together with the flow to calculate left ventricular oxygen consumption and left ventricular uptake of the three substances Each dog was then subjected to cardiac denervation and after three weeks, to allow for endogenous catecholamines to be depleted, a second measurement of the left ventricular blood flow was made using ^{85}Sr microspheres, together with second measurements of coronary AV differences for oxygen content, lactate, glucose and FFA. These measurements were made with the same heart rate, arterial pressure and anaesthetic as in the first study in each dog. In five dogs a third measurement of these variables was made (using ^{95}Nb microspheres) after beta-adrenergic blockade with atenolol. Left ventricular oxygen consumptions in the innervated control study were 109·6±35·7μl O_2 min^{-1} g^{-1}, and after denervation were 141·8±35·7μl O_2 min^{-1} g^{-1}, respectively. This increase in left ventricular oxygen consumption was accompanied by concomitant increases in lactate consumption from 277·4±156·7 nmol min $^{-1}$g^{-1} to 917±213·3 nmol min^{-1}g^{-1}, respectively, but no consistent changes in glucose and FFA uptake. External left ventricular work per ml of oxygen consumed fell from 4·38±0·63 to 2·77±0·92J ($P<0·05$) and for each μmol of lactate consumed fell from 2·004±0·949 to 0·433±0·151J ($0·05>P>0·025$).

This implies that tonic release of noradrenaline from nerve terminals increases the conversion of substrate and oxygen into mechanical energy.

This same effect was achieved by beta-adrenergic blockade after denervation. This leaves the humoral α-adrenergic influence as the sole remaining factor and suggests that the effect is mediated by the α-adrenergic properties of noradrenaline.

Evidence for non-infiltrative neoplastic cardiomyopathy and presence of negative inotropic factor in acute myeloid leukaemia: a clinico-experimental study

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Congestive cardiomyopathy in acute leukaemia is attributed to daunorubicin. In this study, I examined the cardiac function in 12 normal subjects and in 15 patients with acute myeloid leukaemia before and after daunorubicin. The left ventricular end-systolic dimension, ejection fraction, and the end-systolic shortening in relation to the end-diastolic dimension were significantly abnormal in leukaemic patients before cytotoxic therapy. Two patients had left ventricular failure before treatment and 3 others developed heart failure within 4 weeks of diagnosis. Necropsy in 3 of these showed no leukaemic deposits in the myocardium. These results suggest that leukaemic cardiomyopathy is unrelated to drugs or neoplastic infiltration of the myocardium.

In an effort to look for a cardiotoxic substance in leukaemic blood, I fractionated leukaemic serum and blast cell extract in a Sephadex G-15 column. Fractions 8 and 9 had a negative inotropic effect on increased coronary vascular resistance, and decreased oxygen consumption of the isolated rabbit heart. This factor may be related to poor left ventricular function in acute myeloid leukaemia.

Regional myocardial perfusion in dogs and man: continuous measurement by Krypton-81 m. Relation between acute regional ischaemia, electrocardiographic signs, and effects of nitroglycerin

Andrew P. Selwyn
The Royal Postgraduate Medical School,
Hammersmith Hospital, Ducane Road, London
W12 0HS

The physical properties of the inert freely diffusible gas Krypton-81m (half-life 13 s) allow the development of a technique for the continuous observation and assessment of regional myocardial perfusion in dogs and man. The theoretical considerations, an investigation, and a practical validation for the use of ^{81m}Kr were presented.

In 25 dogs the relation between changes in regional coronary flow, using the electromagnetic flow probe and changes in regional counts per minute using ^{81m}Kr was significant ($P \pm < 0{\cdot}001$, $R = 0{\cdot}933$).

The theory and experimental evidence relating the loss of R waves and the development of Q waves to the loss of electrically active myocardium is presented.

In 32 dogs epicardial electrocardiograms and the abnormalities of regional perfusion were recorded before, during, and after 5, 20, 60, and 240 minutes of left anterior descending coronary artery (LAD) occlusion. The natural history and evaluation of the changes in acute regional ischaemia, epicardial ΣST elevation, and the loss of R waves (and development of Q waves) is analysed and presented. The significant beneficial effects of intravenous nitroglycerin and methylprednisolone sodium succinate on acute regional ischaemia (^{81m}Kr), the evidence of acute cell injury (epicardial ΣST elevation), and the progressive loss of electrically acute myocardium (R loss and the appearance of Q waves) is described. These beneficial effects upon the progressive loss of electrically active myocardium could only be shown in the first 2 hours after LAD occlusion.

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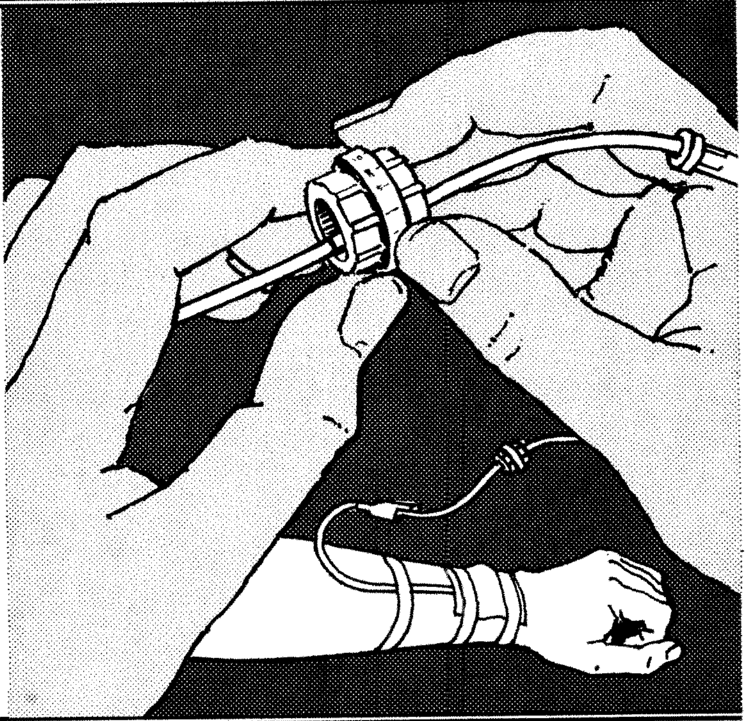

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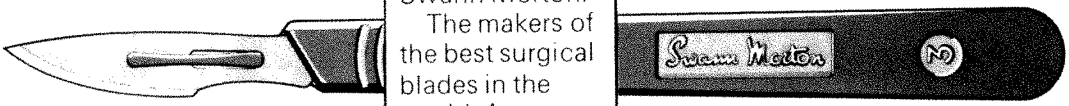

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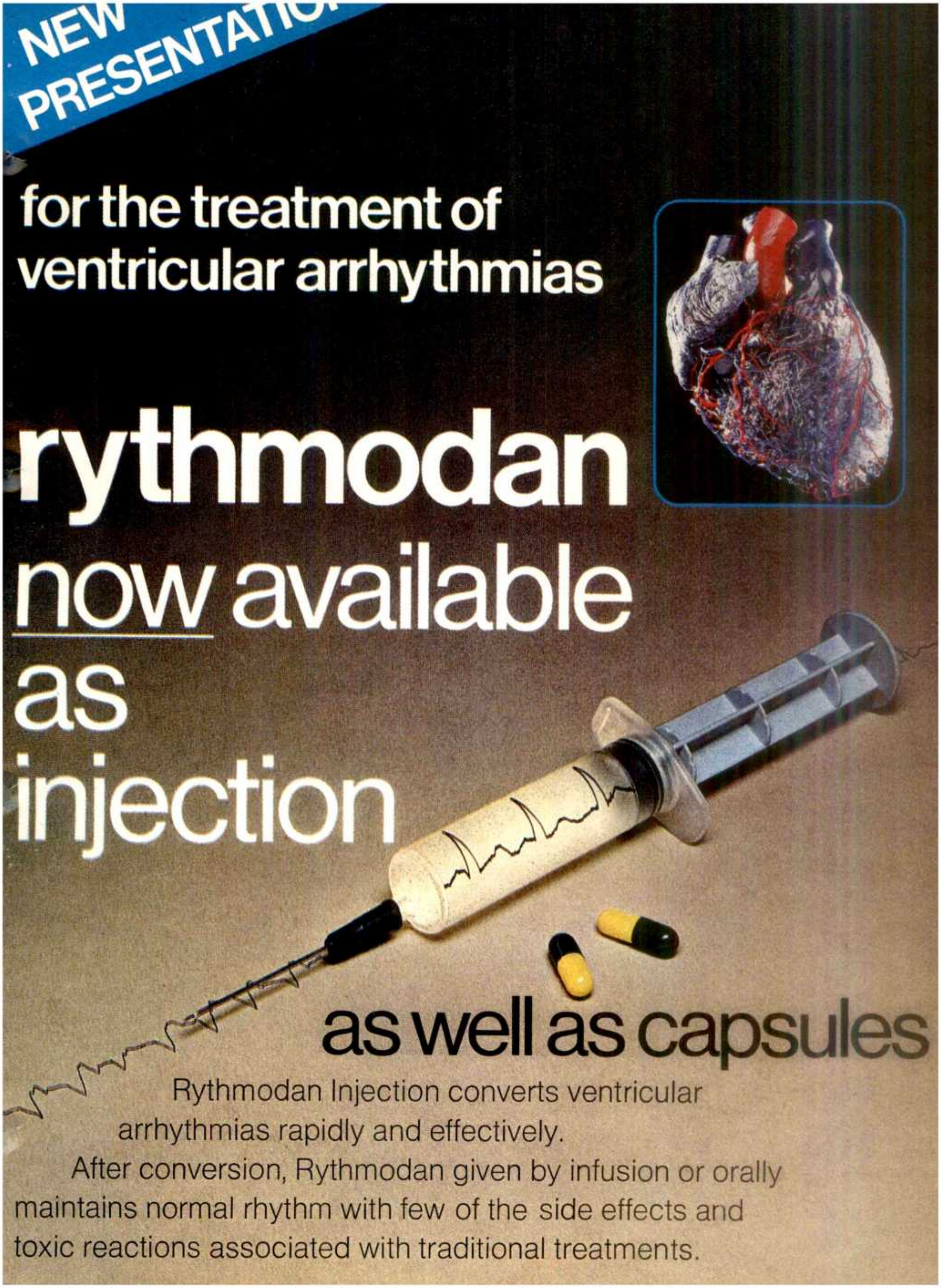

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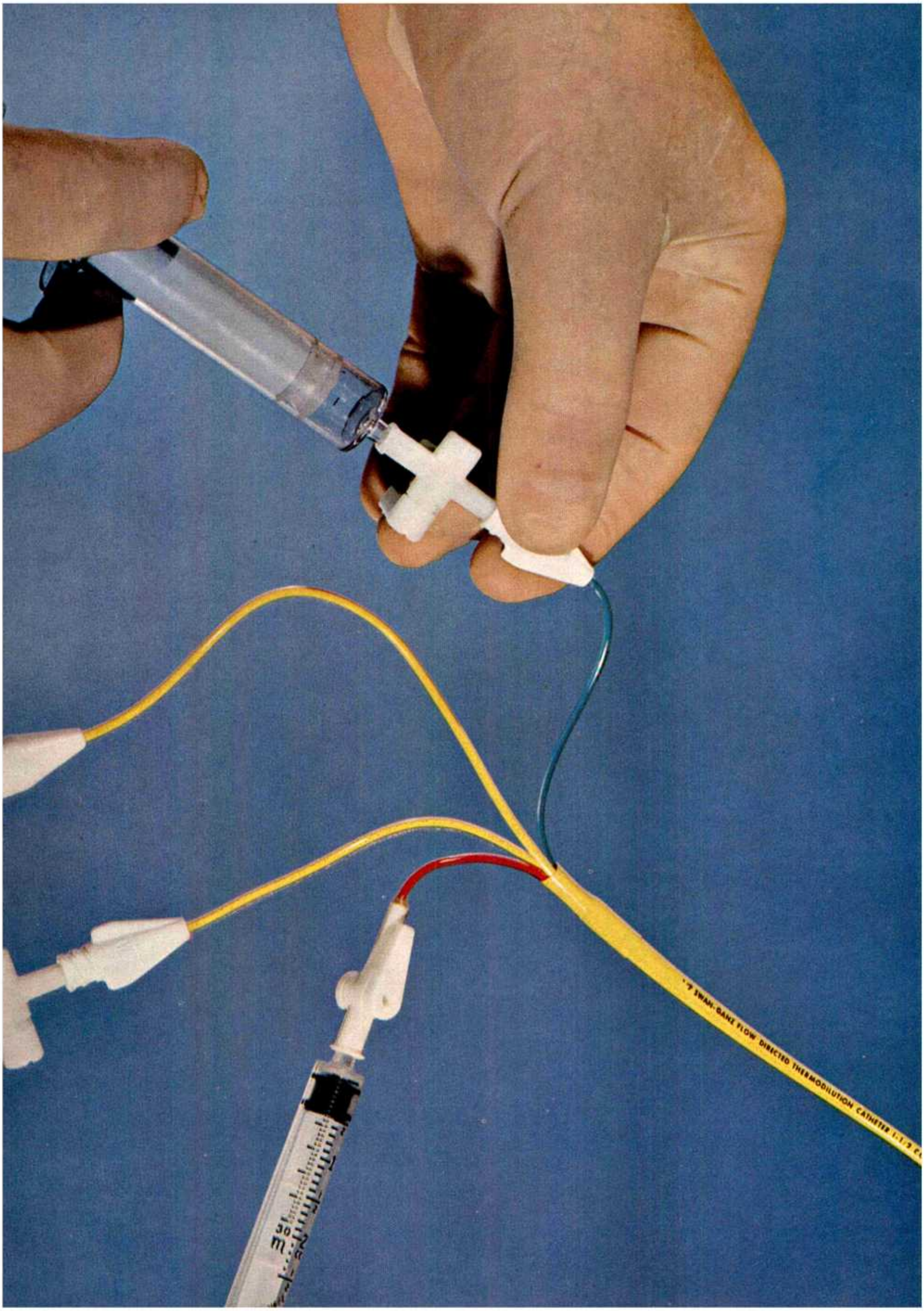
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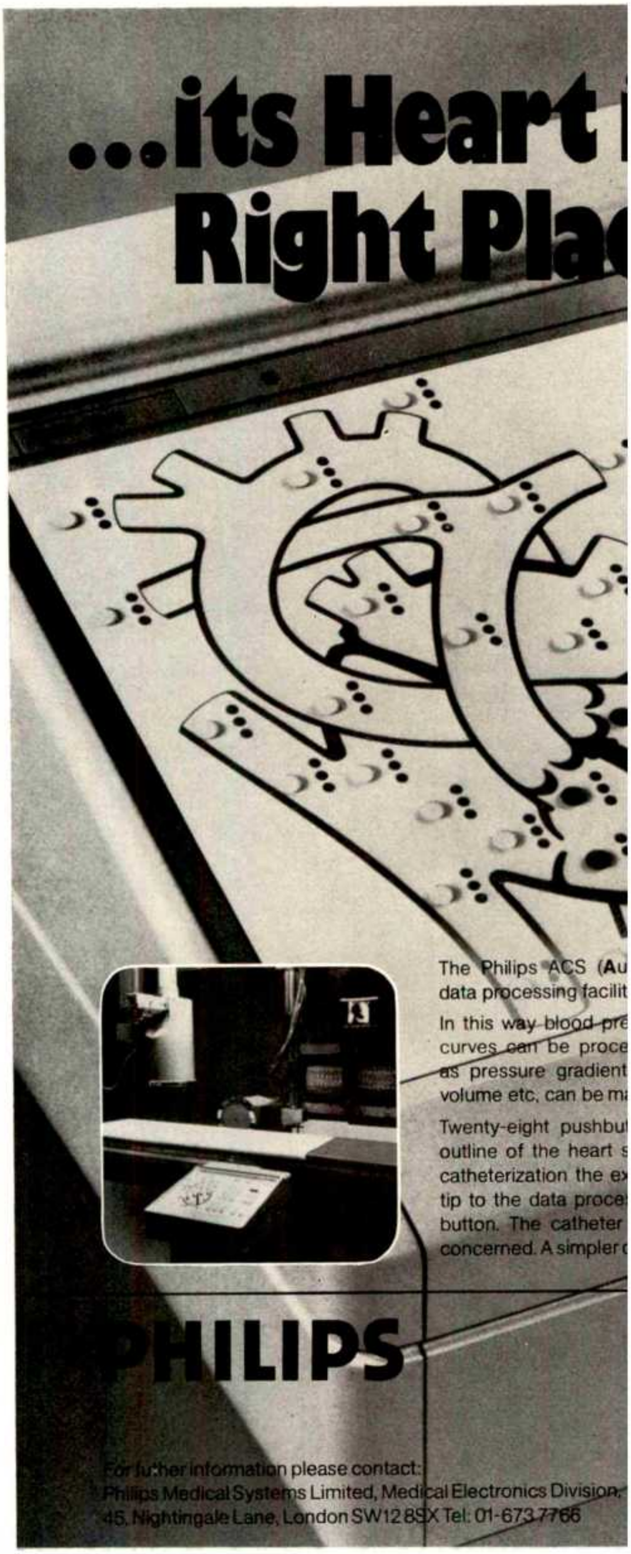

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IN PRINCIPLE

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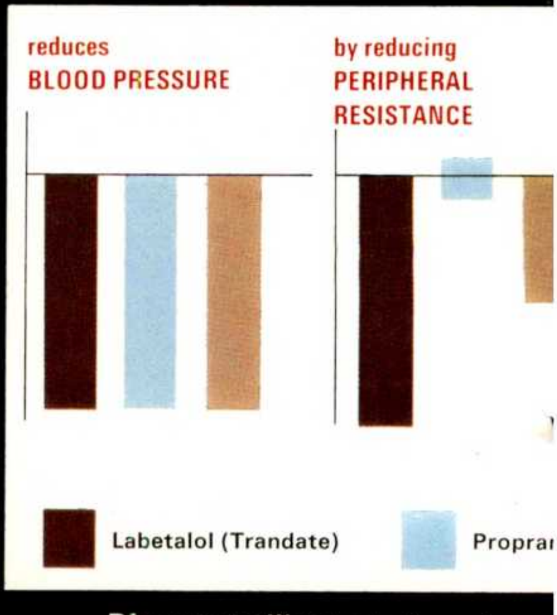

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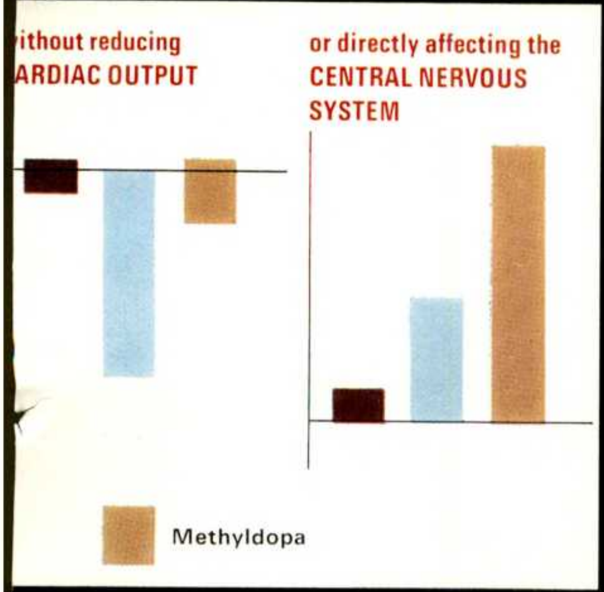

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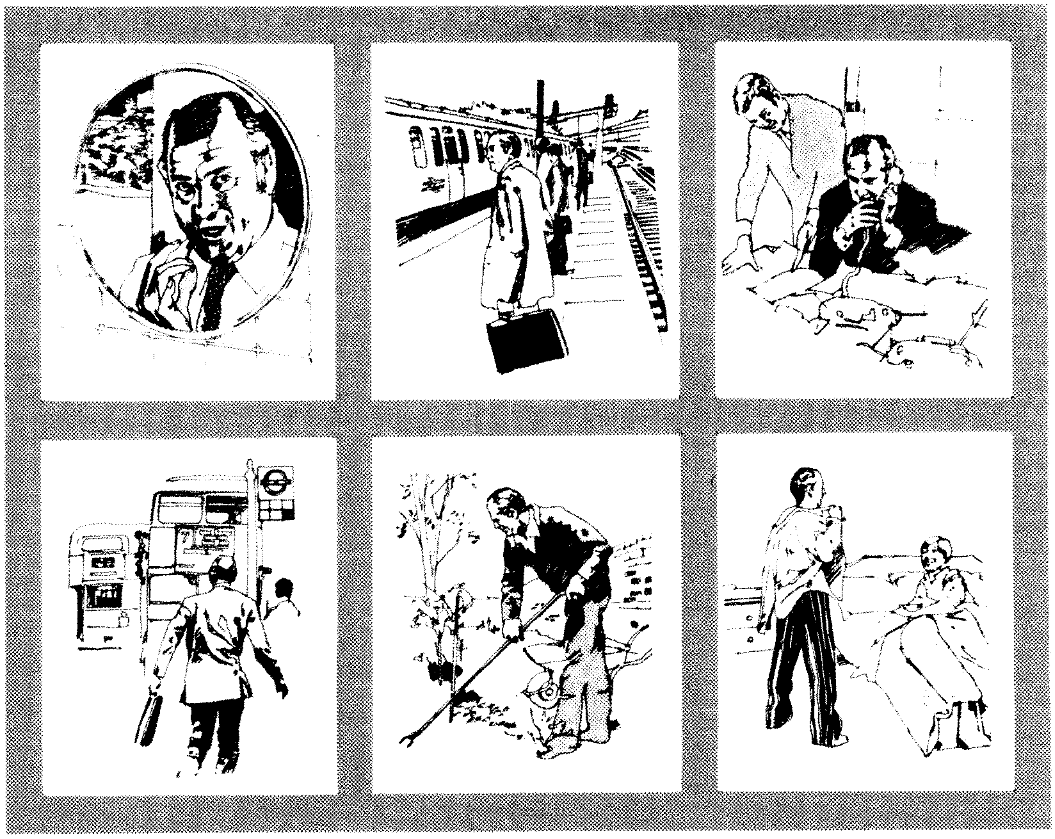

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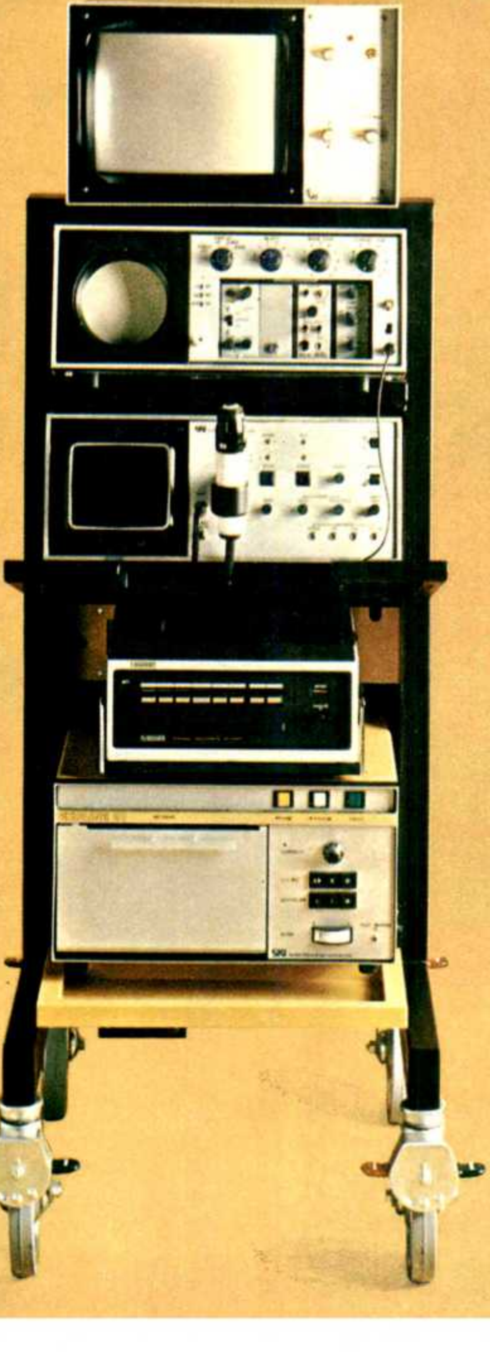

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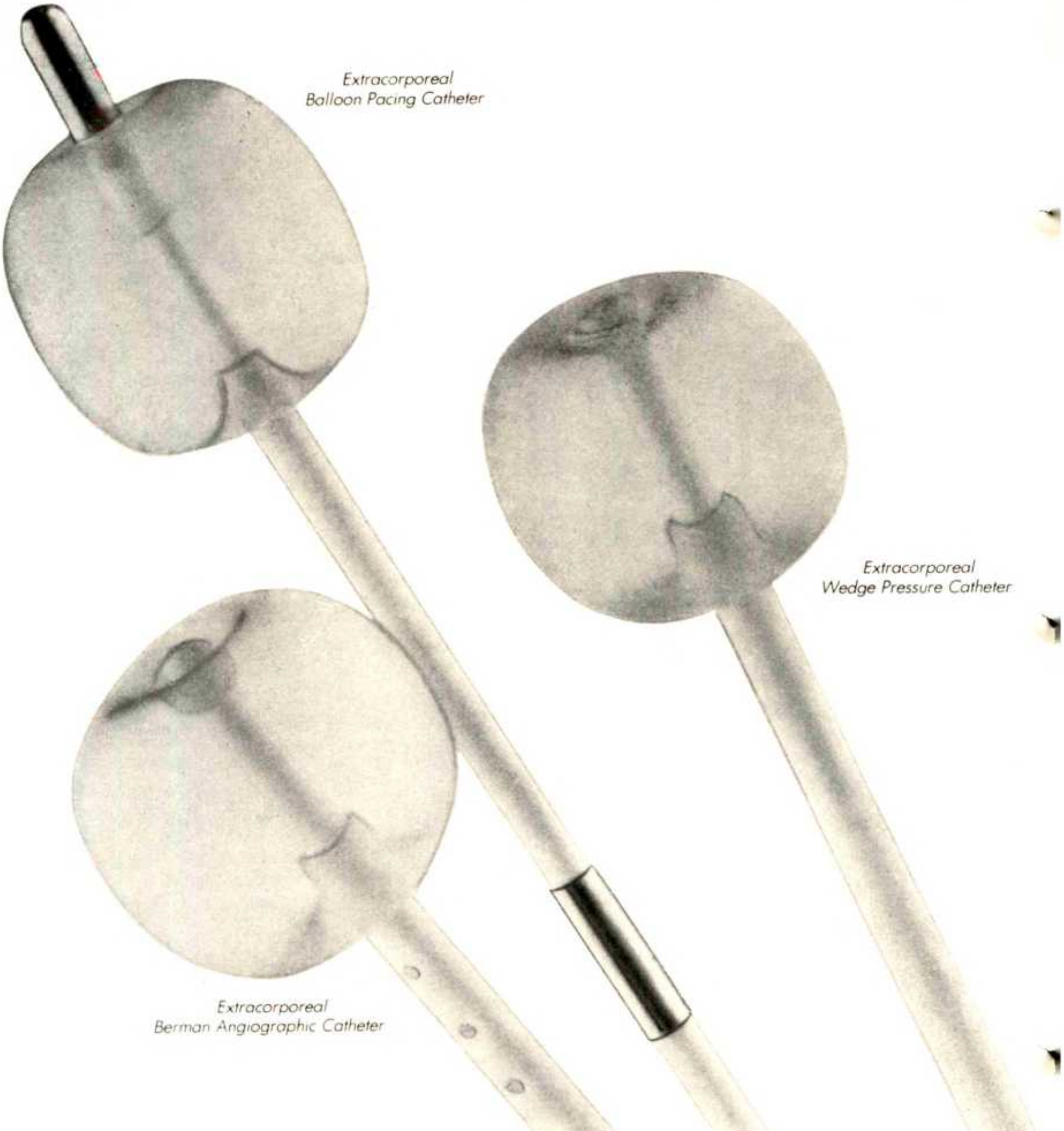

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1. Lancet, 1973, ii, 399 2. Lancet, 1973, ii, 404 3. Amer. Heart J., 1976, *91*, 58 4. Circulation, 1975, 51 & 52, Suppl. II, 147 5. Lancet, 1975, i, 1257 6. Circulation, 1975, 51 & 52, Suppl. II, 199

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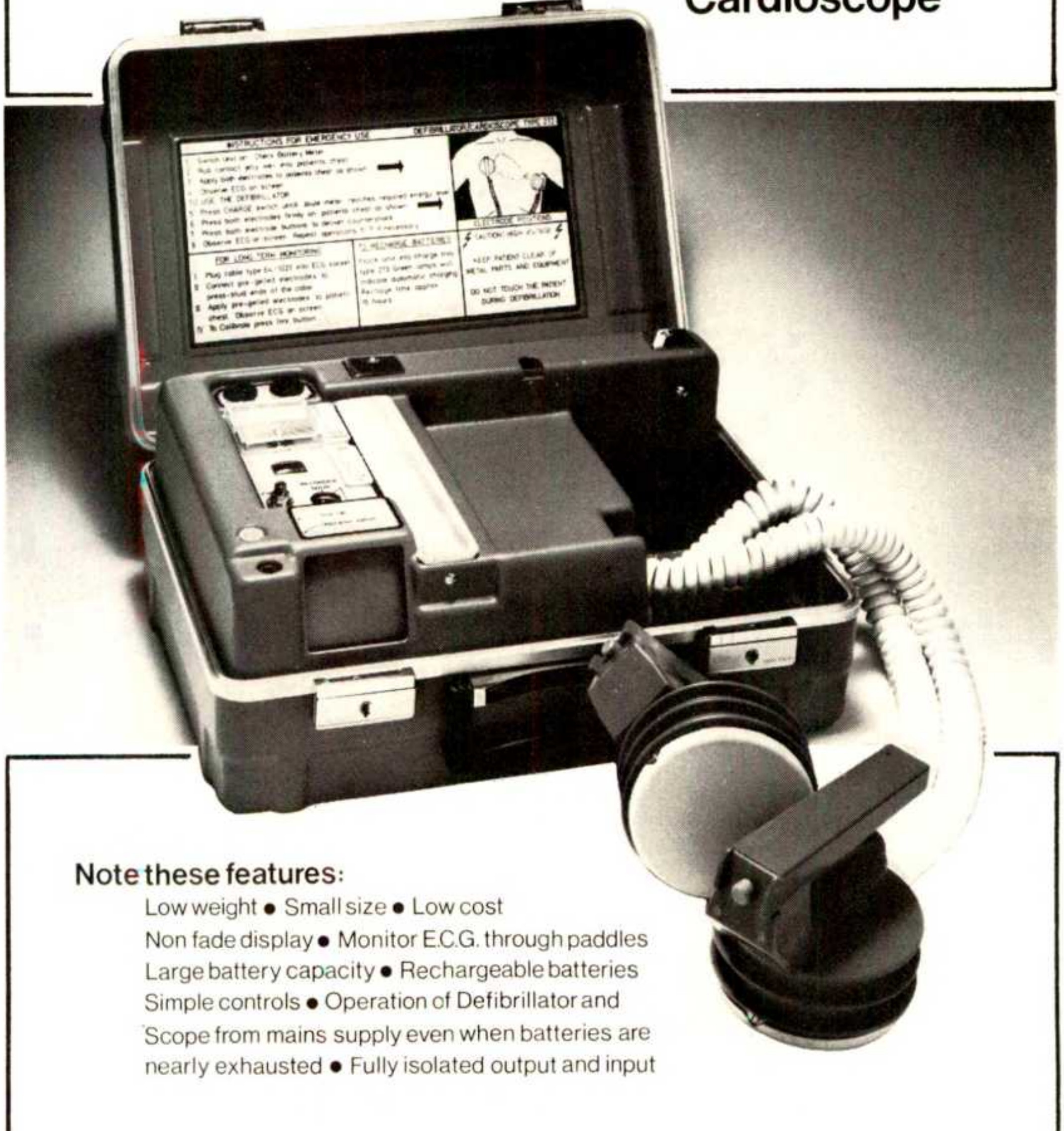

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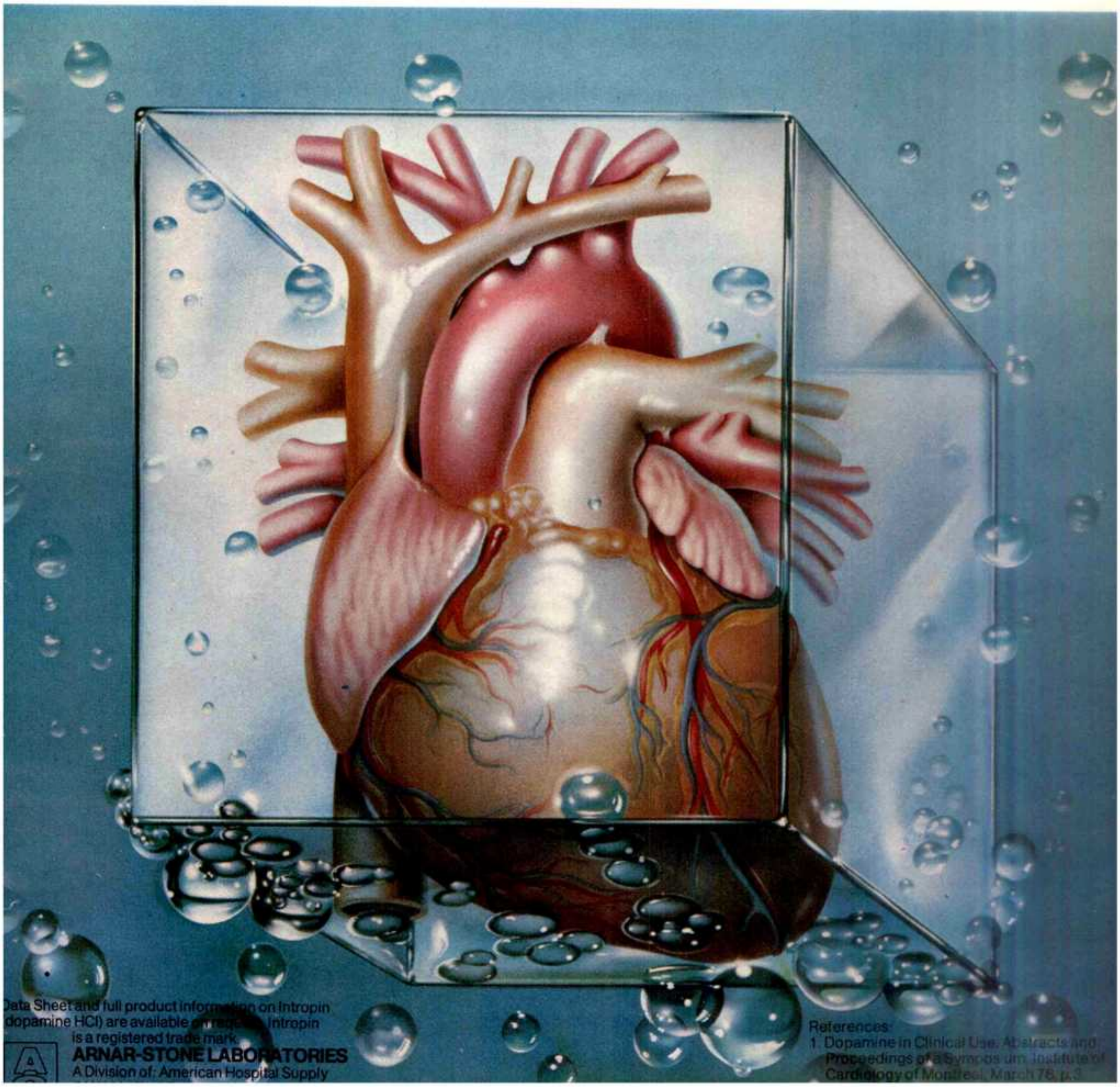

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References:
1. Dopamine in Clinical Use: Abstracts and Proceedings of a Symposium. Institute of Cardiology of Montreal. March 78, p.3

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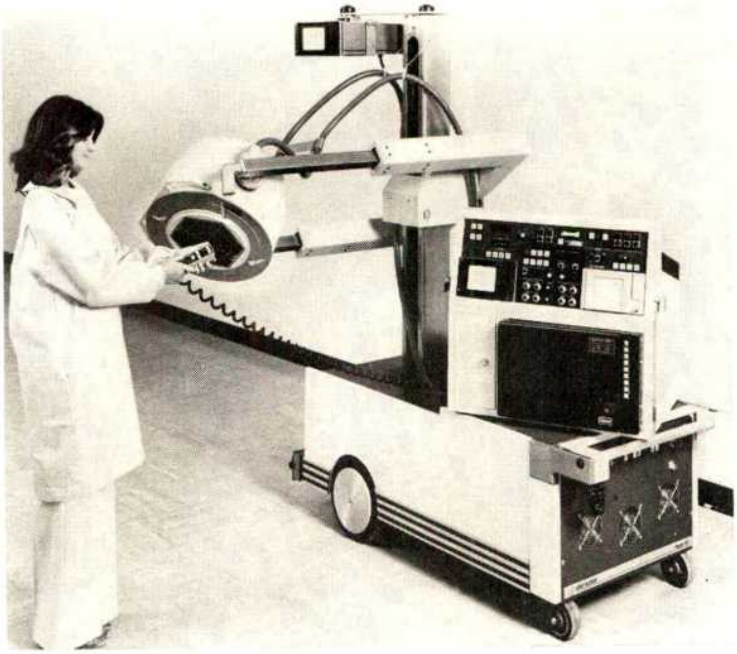

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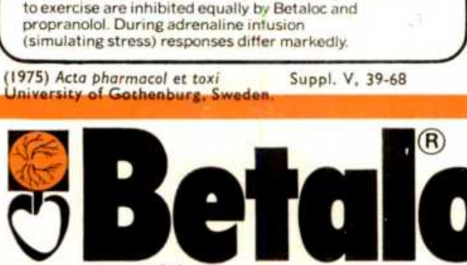
In acute stress[1]

Of particular importance in hypertension—non-selective blockade of peripheral vascular β_2 receptors may permit dominance of the α-receptor (vasoconstrictor) response to adrenaline. The net effect is a drop in cardiac output, with raised peripheral resistance and increased blood pressure. In contrast, selective β_1 blockade allows the β_2 receptors to function normally and so maintains control of blood pressure.



Normally, heart rate and blood pressure responses to exercise are inhibited equally by Betaloc and propranolol. During adrenaline infusion (simulating stress) responses differ markedly.

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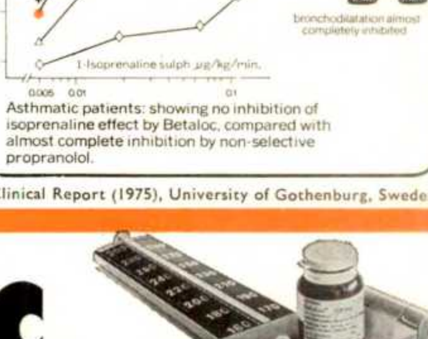

Asthmatic patients: showing no inhibition of isoprenaline effect by Betaloc, compared with almost complete inhibition by non-selective propranolol.

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[1] (1975) *Acta pharmacol et toxi* Suppl. V, 39-68 University of Gothenburg, Sweden.

[2] Clinical Report (1975), University of Gothenburg, Sweden.

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Invited article

British Heart Journal, 1977, **39**, 357–362

The intermediate coronary care unit
A stage in continued coronary care[1]

LEON RESNEKOV

From the Department of Medicine (Cardiology), University of Chicago, Pritzker School of Medicine, Chicago, Illinois, U.S.A.

The concept of continued and progressive coronary care rather than intermediate coronary care is proposed. At each clinical stage the patient may be at risk and his management needs to be planned appropriately—prevention of the development of coronary disease, prehospital care, acute coronary care, subacute coronary care, and late hospital stay. Meticulous continued care once the patient leaves the hospital and returns home may be needed for a long time.

Although the benefit of an intermediate coronary care unit has not yet been proved, significant patient risk continues beyond 12 days of hospital admission. High risk patient subsets are emerging requiring careful continued monitoring and the ability to undertake emergency measures as needed, and this is particularly so in patients suffering large anterior infarction, in those with infarction associated with cardiac failure, when infarction is associated with fascicular block and other types of conduction disturbances, and in patients who continue with rhythm disturbances after their admission to the hospital. Electrocardiograph leads III and V1 displayed simultaneously should be routinely monitored in patients with fascicular blocks and acute anterior infarction as a guide to instituting prophylactic transvenous pacemaking.

The continuation of intensive patient care and monitoring beyond the usual 2 to 5 days in a coronary care unit allows early mobilisation of patients in safety, thus speeding their ultimate rehabilitation.

There is, as yet, no satisfactory study documenting the need for intermediate coronary care units, but much presumptive evidence is available to indicate that this is so. A carefully controlled randomised study would be invaluable.

> 'Keep your enthusiasm, but let strict verification be its constant companion'—Pasteur.

Despite some contrary views (Mather *et al.*, 1971) most agree that coronary care units (CCU) reduce the mortality of acute myocardial infarction provided that the patient survives long enough to be admitted (Meltzer, 1968; Pantridge, 1970; Hofvendahl, 1971; MacMillan and Brown, 1971). In our own CCU an analysis of more than 500 proven cases of acute myocardial infarction has shown a progressive decline of mortality in the acute phases of myocardial infarction from more than 28 per cent before the unit was opened to less than 8 per cent (Resnekov, 1975). The patient who suffers acute myocardial infarction continues at risk even after surviving its first hazardous days after its onset. Indeed, the mortality during the later in-hospital phase of the illness when the patient is usually no longer being cared for in the CCU may be as high as that within the Unit itself (Fig.). In consequence, the concept of intermediate coronary care, or as it is sometimes called 'progressive coronary care' was proposed, whereby patients could be cared for in close proximity to the CCU and where all necessary monitoring equipment would be to hand with personnel trained in the interpretation of arrhythmias and in emergency resuscitation (Gotsman and Schrire, 1968; Grace and Yarvote, 1971; Whipple *et al.*, 1972). Though advocated almost a

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[1] Supported in part by grants from the Myocardial Infarction Research Unit (MIRU), and Specialised Center of Research in Ischemic Heart Disease (SCOR-IHD), and by the Chicago Heart Association.

Received for publication 8 September 1976

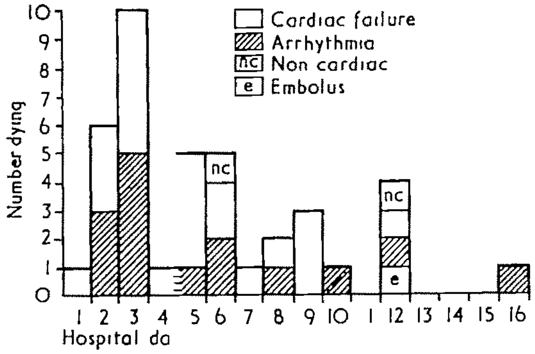

Fig. *Forty-one sequential fatal cases of acute myocardial infarction, showing the days of death and its cause.*

decade ago, there is still considerable controversy about the benefits of such intermediate care units.

It should be recognised that the patient with coronary heart disease continues at risk from the moment the first clinical manifestation becomes apparent. The risk does not end once the patient who has suffered acute myocardial infarct leaves the coronary care unit, after being cared for there for 3 to 4 days. It does not end once he leaves the hospital. Sudden devastating arrhythmias are all too frequent in the weeks or months after recovery from acute infarct, and further infarction may occur suddenly and without warning. Fascicular blocks may be followed by sudden and dramatic deterioration of conduction resulting in sudden death. Perhaps then, appropriate patient care is one of continued management, recognising the particular risks that the patient runs at each stage of his illness, instead of locking our thoughts and practice into a rigid geographical system which for administrative purposes we label as coronary care unit, intermediate care unit, and general medical ward.

HISTORY OF CORONARY CARE

Coronary care units were established as a logical sequel to the successful abolition of ventricular fibrillation in a patient using electrical current (Beck *et al.*, 1947), but almost a decade elapsed before Beck *et al.* (1956) and Reagan *et al.* (1956) reported the successful defibrillation of a patient who had suffered ventricular fibrillation after acute myocardial infarction. The parallel development and refinement of closed chest massage and cardiac resuscitation (Kouwenhoven *et al.*, 1960) also served to spur medical thinking towards coronary care. The third element for the practical implementation of coronary care units, namely electronic monitoring of heart rhythms, was also being developed rapidly at this time, but the fourth element, namely trained nursing staff, able to interpret correctly the electrocardiographic patterns was yet to be realised, and until achieved, was to delay the benefit that should have been provided to patients who were being monitored during the formative phases of coronary care units (Day, 1972).

Eventually the concept of a separate coronary care unit, staffed by nursing personnel trained particularly in the recognition of cardiac rhythm disturbances and in the technique of cardiac resuscitation was brought to fruition. The first such unit in the U.S.A. opened during 1962 (Day, 1963). At almost the same time Brown *et al.* (1963) established a unit in Toronto and other early units were organised in London by Shillingford and Thomas (1964), in New York by Gregory and Grace (1967) and by Julian *et al.* (1964) in Australia.

Exciting as these developments were it soon became apparent that though these units might well reduce the in-hospital mortality after acute myocardial infarction, they could only have a minimal effect on the overall mortality of coronary heart disease (McNeilly and Pemberton, 1968).

Accordingly Pantridge and his group set up a mobile coronary care unit in Belfast during 1966 (Pantridge and Geddes, 1966, 1967). The importance of this concept becomes immediately apparent when one considers that more than 40 per cent of deaths from acute myocardial infarction occur within one hour of the onset of symptoms (McNeilly and Pemberton, 1968). Furthermore, 63 per cent of deaths occurring in middle-aged and younger men happen within one hour of the symptoms developing (Bainton and Peterson, 1963), yet only 16 per cent of patients are admitted to the hospital within the first 4 hours (McDonald, 1968). A mobile coronary care unit was therefore set up to give intensive care to the patient wherever the infarct occurred and as soon as possible after the onset of symptoms (Pantridge, 1970).

Finally, in 1968 the concept of intermediate coronary care emerged with the realisation that the risk of sudden death did not end when the patient was allowed to leave the CCU. It is likely that it was Gotsman and Schrire (1968) who first proposed setting up an intermediate coronary care unit (ICCU). Though no description of a functioning ICCU followed, these authors clearly had in mind continued and progressive coronary care. Grace and Yarvote (1971) began monitoring patients beyond the 5th hospital day as a routine in a specially equipped and staffed area separate from the CCU, and Whipple *et al.* (1972) were also early in developing dedicated units of this type.

As can be appreciated, we are now well along the path of providing the patient continued and uninterrupted specialised care from the moment the clinical effects of coronary arterial disease become manifest, even before the patient arrives at the hospital, and throughout the acute and subacute phases of his illness. We still, however, lack imaginative programmes for continued care once the patient has left hospital and have not yet succeeded in defining each patient's risk of developing a life-threatening arrhythmia or a recurrence of myocardial infarction; much less so their prevention. No doubt careful study and consideration of this later stage of the disease will be as rewarding as the development of mobile coronary care units, coronary care units, and intermediate coronary care areas.

CONTINUED CORONARY CARE

As long as the patient continues at high risk, acute infarction should be treated in hospital according to the following principles:

(1) Patients should be nursed in one area.
(2) Continuous electrocardiographic monitoring and analysis should be available.
(3) Cardiac arrhythmias should be managed appropriately and aggressively.
(4) It should be possible to obtain additional specialised care as needed, including haemodynamic monitoring, circulatory assistance, and emergency surgery.

Consideration of the data from the University of Chicago shown in the Fig. reveal that of 41 fatal in-hospital cases of acute myocardial infarction, 17 (41·5%) occurred between days 1 and 3 of admission, 19 between days 4 and 10 (46·3%), and there were 5 deaths after the 10th day (12·2%). Sixty-seven per cent of deaths occurred in the CCU but 33 per cent occurred after the patient left the Unit and while he was being cared for in an immediately adjacent cardiology ward. The causes of death were cardiac failure in 54 per cent, rhythm disturbances in 40 per cent, and the remaining 6 per cent died as a result of other causes. It will be noted that there is no obvious time pattern for these late deaths and indeed the majority occurred beyond the 5th hospital day. Similar data noting the high incidence of death from acute myocardial infarction after discharge from the CCU have been well documented (Oliver *et al.*, 1967; Hofvendahl, 1971; McGuire and Kroll, 1972; Weinburg and Col, 1972). In our own series, the largest proportion of these late deaths were sudden and unexpected. Subsequent review of patients' CCU courses did not show any definite predictors of sudden death. It is important to realise, however, that by the end of the 10th day after admittance to hospital for acute myocardial infarction, only 75 per cent of all deaths have been accounted for (Grace and Yarvote, 1971). It is clear, therefore, that there is a need for continuing close observation and monitoring of patients beyond the traditional 3 to 5 CCU days.

The usual CCU is not ideal for prolonged patient stay since there is always considerable pressure on the available beds as new patients require to be admitted. Furthermore, medical practice now recommends mobilising patients as soon as possible after acute infarction. This requires additional personnel and modification in monitoring techniques and these are best done away from the CCU.

An intermediate coronary care unit should provide the following:

(1) Continued patient monitoring allowing immediate recognition of cardiac rhythm and conduction disturbances.
(2) Immediate cardiopulmonary resuscitation.
(3) Nursing personnel trained as for those in the coronary care unit.
(4) Early mobilisation.
(5) Definition of individual risk and plans for continued care.

A progressive care unit of this type should be geographically close to the coronary care unit and ideally should share medical, nursing, and paramedical staff. Telemetry electrocardiographic monitoring can be recommended since it eliminates hard wiring and makes it possible for the patient to be mobilised more easily while still under constant electrocardiographic control.

Although many units provide electronic monitoring systems which can be extremely sophisticated, analysis of the information being collected is sometimes less than ideal, and even highly skilled nursing personnel miss important arrhythmias if the system involves their watching oscilloscopes over a prolonged period of time. Some method of computer monitoring can be recommended, but only if it is in real-time and on a beat-to-beat basis so that the nursing and medical staff can be immediately appraised of the cardiac rhythm disturbance, and, furthermore, can obtain from the computer an analysis of premature beats and other rhythm disturbances which have occurred in the immediate past. Several such systems are now available, some of which have been extensively tested in practice and found to be satisfactory in the use (Fozzard and Kinias, 1976).

ARE INTERMEDIATE CORONARY CARE UNITS WORTH WHILE?

Although many units have been set up, very few controlled trials of intermediate coronary care have been reported.

Grace (1975) analysed 136 patients with acute transmural myocardial infarction admitted to the hospital. There were 36 deaths (26·5%). Of these, 32 (89%) occurred in the coronary care unit, 2 (5·6%) in the intermediate coronary care unit, and 2 in the general ward (5·6%). The substantial decrease in mortality outside the CCU compared with the previous reports from the same unit (Grace and Yarvote, 1971) was used to substantiate the role of the ICCU in lowering mortality.

An interesting study was reported by Reynell in 1975, which documented a controlled trial of intermediate coronary care over a 5-year period at a district general hospital. One thousand male patients under 65 years old were allocated at random to a group kept in the same ward as the coronary care unit, and a control group was discharged from the coronary care unit to a general medical ward. Those in the 'intermediate care area' were nursed by the same CCU staff using resuscitation equipment which was immediately to hand. Thus, 520 patients were cared for in the intermediate care area, and 480 were randomised to the general medical ward. Forty-four of the ICCU patients died (8·5%) compared with 43 of the general medical ward patients (9·0%). The difference is not statistically significant. Attempts at resuscitation were made on 35 patients in the ICCU and 41 in the general medical ward. The initial success in the ICCU patients was 46 per cent compared with 22 per cent in those who were being cared for in the general medical ward. The numbers who left the hospital, however, were almost the same; 4 from the ICCU group and 5 from the general medical ward group. From this study it would be hard to conclude that an intermediate coronary care unit had any dramatic impact on in-hospital mortality of acute myocardial infarction, though it must be admitted that the plan of the trial was far from ideal.

Weinberg (1976) has published data comparing the results in 341 patients with acute myocardial infarction cared for during 1969 and 1970 when no ICCU was available, with 354 patients between 1971 and 1972, when an ICCU was operative. He found a 13 per cent CCU mortality between 1969 and 1970 and an 11 per cent CCU mortality between 1971 and 1972. Before the ICCU was opened (1969–1970) the incidence of late hospital deaths was 4 per cent. In 1971 to 1972 with patients being cared for in the ICCU once they had been discharged from the CCU the late mortality was 5 per cent. The two groups were said to have had an equal incidence of rapid or slow arrhythmias, and conduction disturbances. There was no significant difference in heart size, previous infarction, or electrocardiographic localisation of infarction. Once more, it would be hard to conclude that if mortality were the criteria, the case for nursing patients in an ICCU has been proved.

That the patient does continue at risk after discharge from the coronary care unit, continues to be confirmed (Bornheimer *et al.*, 1975). Frieden and Cooper (1976) have documented that an important effect on in-hospital coronary care has followed the introduction of a 22-bed monitored intermediate coronary care unit. The ICCU was established adjacent to an 8-bed coronary care unit and is staffed by the same medical and nursing personnel. Bedside and central station monitoring is available, and, in addition, one area of the ICCU is provided with telemetry electrocardiographic monitoring for the early ambulant patient. Patients remain in the CCU for 2 to 6 days and are then transferred to the ICCU where they remain until the 10th day after admission. Thereafter, uncomplicated patients are transferred to an adjacent special convalescent unit which has no monitors but emergencies can be handled there as needed: 1917 patients were cared for in the ICCU of whom 27 (1·4%) had cardiac arrest and 18 (67%) were successfully resuscitated. The authors believe that the low incidence of cardiac arrest was a result of 24-hour monitoring and the prompt institution of antiarrhythmic therapy by the trained ICCU staff. An interesting additional finding was that the availability of adequately monitored and staffed intermediate coronary care beds allowed an increase in admission to CCU of over 15 per cent. Furthermore, direct admission from the emergency room to the ICCU not infrequently occurred. The duration of hospital stay of patients with acute myocardial infarction was shortened by 3 days using this progressive form of coronary care which also included early mobilisation, and an overall more efficient and successful hospital management of cardiac patients was claimed.

PATIENTS AT PARTICULAR RISK

Although, as already indicated, all patients after acute myocardial infarction should be considered to be at risk of serious arrhythmias and sudden death, it is now clear that certain groups of such patients are more liable to life-threatening situations. Bornheimer *et al.* (1975) who analysed the records of 48 patients dying suddenly and unexpectedly after discharge from the coronary care unit, showed that 25 had myocardial infarction as the sole cause of death, but 23 had additional important features including congestive heart failure.

The following groups of patients are at particular risk and require more intensive and more prolonged monitoring than other patients with acute myocardial infarction:

(1) Those suffering large anterior infarction, usually associated with the development of severe left ventricular dysfunction, or congestive cardiac failure. These lesions usually result from important occlusive lesions of the proximal portions of the left coronary system, and, therefore, a large proportion of the left ventricular myocardium is compromised.
(2) Myocardial infarction associated with cardiac failure. Often these patients have suffered previous myocardial infarction, or systemic hypertension was known to be present.
(3) Myocardial infarction in association with fascicular block. Such patients require very careful electrocardiographic monitoring. It is indeed remarkable that routine electrocardiographic monitoring has been allowed to continue using leads which are inappropriate for monitoring patients with fascicular blocks. Since it is known that sudden and unheralded changes in conduction may occur, information about changes in mean frontal QRS axis, length of PR interval, and the development of bundle-branch block is required. The routine CCU monitoring lead is ill-chosen for this need. In our unit such patients are routinely monitored with standard lead III and lead V1 simultaneously displayed.
(4) Patients who continue with premature beats or other arrhythmias after acute myocardial infarction.

Conclusions

From available published data it will be apparent, therefore, that while the benefit of the intermediate coronary care unit as a separate area of patient management has not yet been proved, patients suffering acute myocardial infarction continue to be at risk even beyond 12 days of hospital care. High risk subsets of patients are now being recognised who require diligent and continued intensive care. It is, therefore, logical to define the risks patients who suffer coronary heart disease run at each stage of their disease and to provide them with continued and progressive care, before, during, and after admission to hospital. With this goal in mind, the 'intermediate coronary care unit' may be defined as an area staffed and equipped as is the coronary care unit and as close to it as possible, not only for the prevention and emergency treatment of life-threatening arrhythmias but also where early ambulation of the patient may begin in safety. Such a progressive care area helps to free beds for the acute myocardial infarct patient without in any way compromising care during the less acute stages of the illness. A carefully controlled randomised study to determine the effectiveness of such continued coronary care would be invaluable.

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Acute coronary insufficiency
Review of 46 patients

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Forty-six patients admitted with acute coronary insufficiency are reviewed. All were investigated by coronary angiography; 4 had normal coronary arteries and are included in this study; the remainder had a distribution of coronary artery disease similar to other angina patients. The clinical and angiographic findings, management, and subsequent course of the other 42 patients are presented. Fourteen patients (33%) in whom rest pain persisted after 48 hours underwent emergency coronary angiography, with 3 deaths; of the surviving 11 who had acute saphenous vein bypass grafting, 2 died at operation and 3 had perioperative myocardial infarctions. Seventeen patients (41%) who initially improved required surgery within 6 months because of symptoms. Eleven patients (26%) were not operated on. It is concluded that acute coronary insufficiency is best managed initially by intensive medical therapy but a high proportion will require surgery later because of disabling angina. Early investigation and surgery are associated with a high mortality and incidence of myocardial infarction. Survivors of surgery are symptomatically improved and there is a low incidence of late infarction and death.

Patients with angina marked by a rapidly progressive course are recognised as having a high incidence of myocardial infarction and death in the immediate future as compared with those with a stable pattern of angina. Because of this, attention has been focused on this group with acute coronary insufficiency especially since the advent of saphenous vein bypass grafting of the coronary arteries.

The optimal method of management in these patients remains uncertain and few long-term studies in which patients have been treated either medically or surgically are available for guidance.

This retrospective report reviews the findings at admission and the subsequent course of 42 patients with acute coronary insufficiency seen at Guy's Hospital from 1 May 1971 to 31 March 1975. During that period it was the policy to perform coronary arteriography on all patients admitted with acute coronary insufficiency after 48 hours of medical treatment if rest pain had not subsided, or before discharge in those who had lost rest pain within 48 hours. The surviving patients have been followed for a mean period of 25·5 months.

Definitions

A patient was considered to have acute coronary insufficiency if the following criteria were fulfilled:
(a) Typical anginal attacks progressively prolonged and severe and occurring with diminishing provocation in a patient either with a previously fixed pattern of angina or with no angina; and/or
(b) One or more prolonged episodes of anginal pain at rest not relieved by trinitrin.
(c) Absence of infarction, enzyme, or electrocardiographic evidence of infarction.

All patients were continuously monitored during at least the initial 48 hours and electrocardiographic abnormalities observed. The changes associated with this condition are T wave inversion or ST segment displacement exceeding 1 mm, without the development of Q waves. Apart from changes observed during monitoring, we were able to record these abnormalities in at least two leads in slightly over half our patients. Patients with cardiogenic shock, valvular heart disease, cardiomyopathy, or normal coronary arteries (see later) were excluded.

The usual definitions of angina and electrocardiographic criteria for myocardial infarction were adopted (Logue and Hurst, 1970). Cardiomegaly was defined as a cardiothoracic ratio of greater than

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0·50 on a posteroanterior chest film. A left ventricular end-diastolic pressure greater than 12 mmHg was considered abnormal. Coronary arterial narrowing of greater than 70 per cent reduction in diameter was regarded as significant. One vessel disease was defined as a significant stenosis affecting one of the following arteries: the left anterior descending or its diagonal branch, the circumflex or its obtuse marginal branch, the right coronary artery or its posterior descending branch. A reduction of 50 per cent or greater in the left main stem coronary artery was regarded as significant.

Left ventricular function was assessed from angiocardiograms taken in the 30° right anterior oblique position and classified as follows: class 0: normal function; class 1: minor general reduction of function; class 2: hypokinetic, akinetic, or aneurysmal area; class 3: moderate general reduction of function with or without class 2; and class 4: grossly reduced function with or without class 2.

Functional classification was according to the N.Y.H.A. criteria.

Patients and methods

Forty-six patients fulfilling the above criteria for acute coronary insufficiency were seen during the relevant period, but the 4 shown on angiography to have normal coronary arteries have been excluded from the following analysis.

All patients were placed on total bed rest and monitored. Beta-adrenergic blocking agents in full doses and sublingual nitrates as required were administered in addition to analgesics. Anticoagulants were not routinely used in the absence of venous thrombosis or embolism.

Thirty-six patients underwent coronary arteriography and left ventriculography on the same admission at a mean time of 6 days later (range 2 to 33 days). Three patients were readmitted for angiography 40 to 70 days after discharge. The remaining 3 had undergone uncomplicated angiography recently, before their angina became unstable. Coronary angiography was originally performed by the Judkins technique (Judkins, 1967) (25 patients) but the Sones method was used more often latterly (Sones and Shirey, 1962) (17 patients).

The patients have been divided into 4 groups based on their clinical course and in particular their response to medical therapy in the first 48 hours.

GROUP 1

Patients who continued to have rest pain after 48 hours despite full medical treatment. There were 14 in this group. Angiography was carried out and the patients operated upon at a mean time of 3 days after admission.

GROUP 2

Patients whose symptoms disappeared with rest and medical treatment but who immediately experienced increasing angina again on mobilisation. There were 10 patients in this group. All were operated upon at a mean time of 29 days after admission.

GROUP 3

Patients whose symptoms disappeared with rest and medical treatment and who were discharged from hospital without significant angina but whose symptoms subsequently returned as they attempted to resume normal activities. There were 7 patients in this group and all were operated upon. The mean time from the first admission was 5·5 months.

GROUP 4

Patients who were not operated upon. There were 8 patients whose pain settled (6 with medical therapy and 2 after infarction) and 3 whose left ventricular function was too poor for operation to be performed.

All except 1 of the surviving patients have been followed at the outpatient clinic, attending every 6 months. For the 1 exception, follow-up data have been obtained from her physician. Of the 32 survivors, 28 have been seen within 1 month before preparation of this report and a full history, examination, electrocardiogram, chest *x*-ray film, and bicycle exercise test were performed. The latest follow-up of the other 4 was by communication with the patient's physician.

Exercise tolerance testing was performed on the Monark exercise bicycle; continuous electrocardiographic monitoring was carried out from an electrode placed in the V5 position. The end-point was taken as fatigue or dyspnoea of such severity that the patient could not continue, or chest pain of a degree that would under usual circumstances cause the patient either to rest or to take glyceryl trinitrate. Results have been expressed as total work performed. ST segment displacement was measured 0·04 s after the J point (1 mm ST depression being regarded as significant).

Statistical analysis was carried out using the χ^2 test, and Student's paired and unpaired t test.

Results

Of the 42 patients, 38 were men and 4 were women. Mean age was 52·6 years (range 30 to 71 years).

Table 1 *Details of patients*

	Group 1	*Group 2*	*Group 3*	*Group 4*	
				Settled	*Inoperable*
Number of patients	14	10	7	8	3
Age—mean and range	50·9	51·7	52·3	59·3	49·0
(y)	30–71	43–62	40–57	44–67	46–51
Angina—mean and range	24	61 9	24·8	61·1	48
(m)	5–72	3–144	2–72	1–60	36–72
Duration of unstable angina—	19 6	16·9	18·5	28·7	9
mean and range (d)	1–35	1–30	4–40	2–35	4–14
Previous myocardial infarction	5	5	2	2	2
Radiographic cardiomegaly	—	1	1	—	2
Left ventricular end diastolic pressure	12	14	11	13	16
mean and range (mmHg)	5–17	4–20	5–25	5–24	8–22
Left ventriculogram—Class 0	2	4	1	1	—
Class 1	6	3	4	6	—
Class 2	2	—	—	—	—
Class 3	4	3	2	1	1
Class 4	—	—	—	—	2
Average number of vessels involved per patient	2·5	2·6	2·5	2·2	2·6
Left main stem lesion	—	2	—	1	2

GROUP 1 (Table 1)

The 14 patients in this group continued to have angina at rest 48 hours after admission despite beta-sympathetic blockade and sublingual nitrates. All except 1 had a previous history of chronic angina, and the mean duration of unstable angina was 19·6 days (range 1 to 35 days). Five patients had suffered previous myocardial infarctions (range 1 to 14 years).

One patient who had coronary angiography 5 weeks previously to investigate chronic angina was not reinvestigated but all the others underwent coronary angiography at a mean time of 49 hours after admission (range 24 to 90 hours). Four patients had angiography within 24 hours after they had been transferred from other hospitals where the diagnosis of unstable angina had been made earlier.

At angiography the mean left ventricular end-diastolic pressure was 12 mmHg (range 5 to 17 mmHg). The left ventricles were classified as normal in 2, class 1 in 6, and either class 2 or class 3 in the remaining 6.

Table 2 *Follow-up of surgically treated patients groups 1 to 3*

	Group 1	*Group 2*	*Group 3*
No. of patients	11	10	7
Operative mortality	2	0	1
Perioperative myocardial infarction	3	2	3
Follow-up of survivors	31·4 mth	19 mth	25 6 mth
—range	9–49 mth	3–33 mth	17–29 mth
Late myocardial infarcts	0	0	0
Late cardiac deaths	0	0	0
Non-cardiac deaths	0	1	1
Late survivors	9	9	5
N.Y.H.A. Class 1	5	5	1
Class 2	3	3	3
Class 3	0	1	1
Class 4	1	0	0
Number of patients with angina	3	3	2

There was an average of 2·5 coronary vessels involved per patient; none in this group had a left main stem lesion. There were 3 deaths related to investigation. Two patients died during angiography, 1 could not be resuscitated after developing ventricular fibrillation; the other patient had intractable pain and was hypotensive before the study. At necropsy both patients had undetected myocardial infarctions approximately 2 weeks old and extensive coronary artery disease. The third death occurred 18 hours after the investigation and followed a short period of chest pain. Necropsy showed a fresh thrombus in the left anterior descending artery. All had been studied by the Judkins technique.

The surviving 11 patients (Table 2) were operated on at a mean time of 3 days after admission. Ten patients had 2 saphenous vein grafts and 1 patient a single graft. Two patients died at operation (18·2%) and an additional 3 (27%) had perioperative myocardial infarcts.

The 9 surviving patients have been followed for a mean time of 31·4 months (range 9 to 49). There have been no late deaths or myocardial infarcts. Five of the 9 survivors are free of pain and on no medication, 3 are N.Y.H.A. class 2 and 1 patient is N.Y.H.A. functional class 4.

Postoperative angiography in 3 patients showed that all the 6 grafts were patent. Two of these patients are pain free; the other showed progression of the disease, and is the patient in class 4.

Seven patients have recently been exercised at a mean time of 31·4 months after operation (Table 3). Preoperative exercise tests were naturally not avail-

Table 3 *Exercise tests*

	Group 1		*Group 2*		*Group 3*		*Group 4 (settled)*	
	Preop	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*	*Initial*	*Recent*
Time of test		31·4		19		25·6		18
—mean and range (mth)		9–49		3–33		17–29		3–30
Number of patients	0	7	5	5	5	5	6	6
Mean total kpm	—	3447	1770	4166	1666	2416	1890	2613
—standard deviation ±	—	1056	693	3156	1327	1192	1301	879
More than 1 mm ST depression with exercise	—	1	5	1	1	0	3	2
Angina during exercise	—	1	5	0	4	0	4	2

able for comparison. The average work performed was 3447 kpm; 3 patients were stopped by dyspnoea and 4 by fatigue. One of the patients experienced angina with ST depression.

Of the 9 operative survivors 6 are working full-time, 2 are retired but active; and the remaining patient is in functional class 4.

GROUP 2 (Table 1)

The 10 patients in this group improved on medical treatment but relapsed on resuming activities and were operated on during the same hospital admission. All patients had a history of previous angina with a recent unstable period of mean 16·9 days (range 1 to 30 days). Five patients had suffered a previous myocardial infarct (range 2 to 11 years).

Angiocardiography was performed on these patients at a mean time of 6·6 days from admission (range 2 to 18 days), and there were no deaths. The mean left ventricular end-diastolic pressure was 14 mmHg (range 4 to 20 mmHg). Four patients had normal left ventricular angiograms, 3 had class 1, and 3 had class 3.

There was an average of 2·6 vessels involved per patient; 2 patients had significant main stem disease as well as major lesions elsewhere.

The 10 patients (Table 2) were operated on at an average time of 29 days after admission (range 12 to 45 days). Two patients had 3 grafts, 7 had 2 grafts, and 1 had an internal mammary artery implanted. Operative mortality was nil and the perioperative infarction rate was 2 (20%). Follow-up has averaged 19 months (range 3 to 33 months). One late death has occurred from malignancy; there have been no late myocardial infarcts.

Five of the 9 survivors are free of symptoms and take no drugs (Table 2). Three are class 2, 2 with mild angina and 1 with dyspnoea. One is class 3 with angina and breathlessness.

One patient has been recatheterised and has 1 of the 2 patent grafts (functional class 2). Five patients had a preoperative exercise test (Table 3), the mean work performed was 1770 kpm, with 1 mm ST depression or greater in all 5. Exercise was stopped in every patient by angina. Recently they have been re-exercised (mean time 19 months after operation); the mean work performed was 4166 kpm but the improvement was not statistically significant. All patients were stopped by fatigue; none experienced angina though 1 showed ST displacement of 2 mm. Seven of the 9 surviving patients in the group have resumed work.

GROUP 3 (Table 1)

The 7 patients in this group improved sufficiently to be discharged from hospital on medical treatment for angina but remained incapacitated and coronary bypass surgery was performed later. All patients had a history of chronic angina; the mean period of unstable angina was 18·5 days (range 4 to 40 days). Two patients had suffered previous myocardial infarction (range 2 to 8 years). Two patients were in left ventricular failure.

Angiocardiography was performed at a mean time of 17·2 days (range 2 to 40 days). The mean left ventricular end-diastolic pressure was 11 mmHg (range 5 to 25 mmHg), 1 patient had a normal ventricle, 4 had class 1 ventricles, and 2 had class 3 ventricles.

There was an average of 2·5 vessels involved per patient. A left main stem stenosis was not found.

Surgery was performed at a mean time of 5·5 months (range 3 to 12 months) in the 7 patients (Table 2). Six patients had 2 grafts, and 1 patient a single graft and plication of a left ventricular aneurysm. Three patients had myocardial infarcts in the perioperative period (42·8%), 1 of whom died, giving an operative mortality of 14·2 per cent.

The surviving patients have been followed for a mean time of 25·6 months (range 17 to 29 months). There has been 1 late death after the patient was brought to hospital with the clinical features of venous thrombosis in the left leg and pulmonary embolism. The electrocardiogram did not show myocardial infarction. We have classified this patient as 'non-cardiac death'. Of the remaining 5 patients, 1 is symptom-free, 3 are N.Y.H.A. class 2 (1 with angina, 2 with dyspnoea). One is class 3 with angina and dyspnoea.

The 5 surviving patients were exercised preoperatively and achieved a mean total work of 1666 kpm (Table 3). Four had chest pain and 1 had ST depression greater than 1 mm. These patients have been re-exercised after an average of 25·6 months. The mean total work was 2416 kpm; the improvement is not statistically significant; no patient had ST segment changes or chest pain. Four of the 5 patients have returned to work.

GROUP 4 (Table 1)

This group consisted of 11 patients who were not operated on. Eight settled during medical treatment. The remaining 3 did not become free of pain but were not considered surgical candidates because of poor left ventricular function. Of the 8 patients who settled during medical treatment all except 1 were men, and the average age was 59·3 years. Only 2 had angina of recent onset and the mean duration of unstable angina was 28·7 days. Two had suffered previous myocardial infarcts 4 years previously and a further 2 had myocardial infarcts after admission at 48 hours and 7 days.

Angiocardiography was performed on all patients at a mean time of 16·2 days after admission (Table 1). The mean left ventricular end-diastolic pressure was 13 mmHg. One patient had a normal left ventriculogram, 6 a class 1 ventricle, and 1 a class 3 ventricle.

There was an average of 2·2 vessels involved per patient and an additional left main stem stenosis was found in 1 patient. Single vessel involvement was found on one occasion.

During the follow-up period (Table 4) of mean 18 months (range 3 to 30 months) there has been 1 late myocardial infarction and 1 cardiac death. One patient is N.Y.H.A. functional class 1 and 5 are class 2. All have angina. The remaining patient is class 3. All patients are taking beta-sympathetic blockers.

Six patients were recently exercised, mean work performed was 2613 kpm, 2 patients showed ST depression, and 2 were stopped by angina (Table 3). In the initial exercise test mean work performed was 1890 kpm, 3 showed ST depression, and 4 were stopped by angina. All patients were improved in comparison to their initial exercise test but this result was not statistically significant.

Table 4 *Follow-up of medically treated patients—group 4*

	Settled	*Inoperable*
No. of patients	8	3
Follow-up—mean and range (mth)	18 3–30	8 6–10
Myocardial infarction—early	2	0
—late	1	1
Cardiac deaths—early	0	0
—late	1	1
N.Y.H.A. Class 1	1	0
Class 2	5	0
Class 3	1	2
Class 4	0	0
Number of patients with angina	7	2

Three patients continued to have pain after admission but were not operated on because of poor left ventricular function (Table 1). Their mean age was 49 years, they had a history of angina of an average of 48 months, and an unstable pattern of mean 9 days. Two had suffered previous myocardial infarcts (range 3 to 10 years). At angiocardiography (Table 1) the mean left ventricular end-diastolic pressure was 16 mmHg; 1 had a grade 3 ventricle and 2 had grade 4 ventricles. There was an average of 2·6 vessels involved per patient. A significant left main stem lesion was found in 2 patients.

One patient has died 12 months after presentation after a myocardial infarct, the other 2 have been followed for 8 months. Both are N.Y.H.A. class 3 (Table 4).

STATISTICAL ANALYSIS

The 4 subgroups were analysed statistically for significant differences in age, duration of angina, duration of unstable pattern, previous infarction rate, end-diastolic pressure, left ventricular pressure and function, number and distribution of vessels involved including left main stem stenoses. No statistical differences were found except that group 2 had a significantly longer duration of angina than groups 1 and 4 ($P < 0·05$).

CORONARY INSUFFICIENCY WITH NORMAL CORONARY ARTERIOGRAPHY

Although patients with the clinical picture of unstable angina who were subsequently shown to have normal coronary arteries have not been included in the above analysis, 4 such cases were admitted during the period covered. There were 3 women and 1 man. All settled within 48 hours and none infarcted. At recent follow-up all continued to have angina but 2 reported an improvement. Thus 8·7 per cent of our 46 patients admitted with a clinical and electrocardiographic diagnosis of acute coronary insufficiency were shown to have normal coronary arteries.

Discussion

The aspect of the natural history of coronary artery disease presented in this paper has been discussed in medical papers for many years under a variety of names, including impending coronary occlusion

(Sampson and Eliaser, 1937), coronary failure (Freedberg *et al.*, 1948), intermediate coronary syndrome (Graybiel, 1955), acute coronary insufficiency (Master *et al.*, 1956), status anginosus (Papp and Smith, 1960), preinfarction angina (Fowler, 1971), and unstable angina (Conti *et al.*, 1973). The absence of a uniform definition and long-term follow-up and, until lately, angiographic correlation has given no sound basis on which to compare the 2 forms of treatment, medical and surgical. The problem of definition has recently been discussed by Chahine (1975). He suggested that the term unstable angina be adopted for these patients, and because of their differing presentation and prognosis they should be subgrouped, thus allowing proper comparison of different methods of treatment.

Some early series of medically treated patients reported a high infarct rate and a mortality of up to 36 per cent (Levy, 1956; Nichol *et al.*, 1959; Beamish and Storrie, 1960; Wood, 1961; Vakil, 1964). Contemporary series, however, of medically treated patients have reported lower infarct and mortality rates. Krauss *et al.* (1972) have reported a 6 per cent incidence of myocardial infarction with a one-year mortality of 15 per cent, and Gazes *et al.* (1973) a 21 per cent incidence of infarction at 8 months and an 8 per cent mortality at 1 year, with a 5·2 per cent yearly mortality over 10 years. Fulton *et al.* (1972) in a series of 167 patients found a 14 per cent incidence of myocardial infarction and a 2 per cent mortality at 3 months. All of these series suffer from the disadvantage that coronary angiography was not performed.

In recently reported series in which coronary angiography has been performed on all patients, coronary artery disease has usually been confirmed. However, some authors have reported the absence of coronary artery disease in patients with unstable angina (Scanlon *et al.*, 1973), and we found 4 such patients during the period covered by this report. These 4 patients have been excluded from the analysis, and are being reported elsewhere.

Although recent reports of series of patients with unstable angina have been supported by coronary angiography, most patients have gone on to surgery and, therefore, knowledge of the true natural history of this condition remains unknown. Angiographic data have confirmed that most of these patients have severe coronary artery disease but they are not as a group distinguishable anatomically from other patients with symptomatic coronary artery disease. Of 408 patients with angiographically documented coronary artery disease and unstable angina reported in 8 series (Lambert *et al.*, 1971; Cheanvechai *et al.*, 1973; Conti *et al.*, 1973; Fischl *et al.*, 1973; Scanlon *et al.*, 1973; Segal *et al.*, 1973; Bonchek *et al.*, 1974; Berndt *et al.*, 1975), 25 per cent had significant obstruction of 1 vessel, 34 per cent of 2, and 41 per cent of 3, this distribution being similar to that reported for groups of patients with stable angina who have suffered myocardial infarction (Bruschke *et al.*, 1973).

The high mortality and infarct rate in patients with unstable angina (Levy, 1956; Nichol *et al.*, 1959; Beamish and Storrie, 1960; Wood, 1961; Vakil, 1964) has led to initial enthusiasm for saphenous vein bypass grafting, but as yet surgery has not been shown to be superior to medical treatment. The operative mortality in 361 cases reported in recent series (Lambert *et al.*, 1971; Cheanvechai *et al.*, 1973; Conti *et al.*, 1973; Fischl *et al.*, 1973; Scanlon *et al.*, 1973; Segal *et al.*, 1973; Bonchek *et al.*, 1974; Berndt *et al.*, 1975) was 9·4 per cent and the perioperative infarct rate 13 per cent. Of the 180 patients who survived surgery and who have been followed for more than 1 year (Conti *et al.*, 1973; Fischl *et al.*, 1973; Segal *et al.*, 1973; Bonchek *et al.*, 1974; Berndt *et al.*, 1975), there has been a late mortality of only 1 per cent per year during a follow-up period of 16 months.

The patients described here are not significantly different from those reported in recent series. They are middle-aged, mainly men, and most have a long history of angina. The incidence of an average of 2·5 diseased vessels per patient is similar to other series but the incidence of 1-vessel disease is lower.

The angiographic mortality of 7 per cent occurred in patients who were being investigated during the acute phase because of continuing pain and we regard the investigation of these patients as hazardous because it may be impossible to exclude patients who have actually infarcted very recently. This is clearly an additional risk whenever investigation with a view to surgery is considered. Several authors, however, have reported no deaths from angiography (Scanlon *et al.*, 1973; Bonchek *et al.*, 1974). We recognise that our subgroups contain small numbers, but in all, operations were performed on 28 patients who either continued to have rest pain (group 1) or were incapacitated by angina despite medical treatment when they resumed activities (groups 2 and 3). The operative mortality of 10·7 per cent is comparable with the surgical series referred to but the perioperative incidence of myocardial infarction is higher. This may be because of differing criteria.

Group 1 patients in this series are comparable with Gazes *et al.*'s (1973) medically treated high risk subgroup in that they continued to have pain 48 hours after admittance to hospital. At 3 months these authors found a mortality of 22·5 per cent, with a 35 per cent incidence of myocardial infarction. The probability of surviving 1 year was 57 per cent and 3 years 37 per cent. Our surgically managed group 1 patients had an operative mortality of 18·1 per cent and a perioperative myocardial infarction incidence of 27 per cent, so if we assume our patients are similar to those of Gazes, the surgical aim of preventing early myocardial infarction and reducing mortality in these high risk patients has not been achieved. During the 31-month follow-up period, however, there have been no further myocardial infarctions or deaths. In a recent progress report of a prospective randomised trial on surgical versus medical treatment in unstable angina, Bertolasi *et al.* (1975) have noted a significantly lower early occurrence of myocardial infarction and death in surgically managed patients. Preliminary results from a further randomised trial (Conti *et al.*, 1975) have shown no difference in mortality rate between medically and surgically treated groups and though the surgical group was symptomatically better they had a higher incidence of myocardial infarction.

There was no surgical mortality among the patients operated on subacutely (group 2) though the myocardial infarction incidence (20%) remained high. They had responded initially to medical therapy but relapsed when mobilisation was attempted. Beta blockade and bed rest were continued, allowing these patients to stabilise before operation was undertaken electively. Fischl *et al.* (1973) have found a similarly low operative mortality in patients with unstable angina managed in this way. Because of the variability of response to beta blockade it is important to adjust dosage individually and in this way many patients with unstable angina may be carried through the acute phase allowing surgery to be performed, if required, electively.

Seventeen (40·5%) of our patients who did not require surgery acutely by our criteria came to operation because of symptoms within 6 months. Similar experience has not been commented upon by other authors. When compared with patients who had settled with medical therapy and did not later require surgery no features were found which would allow the early identification of these patients.

The surgically treated patients in this series followed for a mean time exceeding 2 years have had a low incidence of late myocardial infarction and death. Reports of other surgical series (Conti *et al.*, 1973; Fischl *et al.*, 1973; Segal *et al.*, 1973; Bonchek *et al.*, 1974; Berndt *et al.*, 1975) have also found similar results. It is general experience that among surgical survivors there is a high incidence of asymptomatic patients. The figure is 47 per cent in this series and 57 per cent in those previously referred to (Lambert *et al.*, 1971; Cheanvechai *et al.*, 1973; Conti *et al.*, 1973; Fischl *et al.*, 1973; Scanlon *et al.*, 1973; Segal *et al.*, 1973; Bonchek *et al.*, 1974; Berndt *et al.*, 1975). The improvement has been supported by objective evidence from exercise testing in the individual patients, and is in contrast to the 11 per cent asymptomatic patients in our medically treated group 4.

CONCLUSIONS

(1) Patients with acute coronary insufficiency have similar distribution of coronary artery disease to other angina patients. Almost 9 per cent of our cases had normal coronary arteries but the remainder had an average of 2·5 vessels severely stenosed.

(2) The acute stage can often be managed with bed rest and medical therapy: 60 per cent of our 42 cases improved initially; however 40 per cent required early surgery because of severe pain when they returned to activity. Because of this it is now our policy for all patients with acute coronary insufficiency to have coronary arteriography before leaving hospital.

(3) Patients who survived surgery were largely symptom-free, without drugs, whether the operation had been performed acutely or after a short delay. Exercise testing confirmed the absence of angina, but though the work performed had increased this did not reach statistical significance.

(4) There is a low incidence of late infarction and death among surgically treated patients.

(5) Emergency investigation and saphenous vein bypass grafting carries a high risk. We recommend these procedures are delayed in all patients whose pain is settling on medical treatment.

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Postextrasystolic T wave changes and angiographic coronary disease

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The significance of postextrasystolic T wave changes in beats following induced extrasystoles was assessed by angiography in 55 patients. These T wave changes were found in 81 per cent of coronary artery disease patients but also in 68 per cent of patients with normal coronary arteries (PNS). All patients with normal baseline electrocardiograms and normal coronary arteries showed postextrasystolic T wave changes. In electrocardiographic leads corresponding to the distribution of major coronary arteries, T wave changes occurred just as frequently when the artery was normal (54%) as when the artery was stenosed (55%). Left ventricular asynergy was not associated with an increased frequency of postextrasystolic T wave changes and in fact ejection fraction was greater and end-diastolic pressure lower in patients with T wave changes. Thus, postextrasystolic T wave changes appear not to be useful in diagnosing or localising coronary artery disease.

Postextrasystolic T wave changes (T changes) have been ascribed to cardiac, or specifically to coronary artery disease (von Kapff, 1932; von Fernbach, 1934; Scherf, 1944; Ashman *et al.*, 1945; Levine *et al.*, 1952; Mann and Burchell, 1954; Childers, 1966; McLachlan, 1962; Edmands and Bailey, 1971). However, surveys before the advent of cardiac angiography have not achieved a consensus as to the diagnostic significance of T changes (Fagin and Guidot, 1958; Robitaille and Phillips, 1965). Accordingly, patients with T changes following induced extrasystoles were evaluated by angiography for associated coronary artery disease and ventricular dysfunction.

Subjects and methods

Fifty-five patients were studied in the postabsorptive state during cardiac catheterisation. Thirty-seven patients had baseline ST segment or T wave abnormalities, including 2 because of right and one because of left bundle-branch block.

Electrocardiograms were recorded at 0·1 to 20 Hz with a paper speed of 25 mm/s. Before angiography, a catheter in the left ventricle was manipulated to induce extrasystoles. At least two single ventricular extrasystoles with compensatory pause were recorded in each of the 12 standard electrocardiographic leads.

Left ventriculography and coronary arteriography were performed in all patients. Asynergy was diagnosed if there was a segmental abnormality of systolic wall motion in the right anterior oblique projection. Mitral prolapse was diagnosed if there was protrusion of a portion of the posterior mitral leaflet beyond the mitral annulus during systole. Significant coronary artery disease was defined as ≥ 70 per cent luminal narrowing of one or more major vessels.

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Postextrasystolic beats were analysed for T wave changes without knowledge of the angiographic diagnosis. T change was considered present if there was an alteration in vector, amplitude, or contour as compared with sinus beats. Only postextrasystolic beats with unchanged QRS were considered, in order to obviate consideration of T changes secondary to aberrancy. Fig. 1 to 3 illustrate the spectrum of T changes observed.

T changes were classified according to lead groups thought to correspond to the right coronary artery (II, III, aVF) and left anterior descending artery (I, aVL, V1-6). The circumflex artery was not analysed because of uncertainty as to which leads were appropriate to examine (Williams *et al.*, 1973). Recognising that the right praecordial leads best represent the septum and that septal wall motion was not visualised in the projection used, lead groups were analysed for corresponding asynergy as follows: inferior wall from mitral annulus to papillary muscle insertion (II, III, aVF); anterior wall, and apex (I, aVL, V1-6).

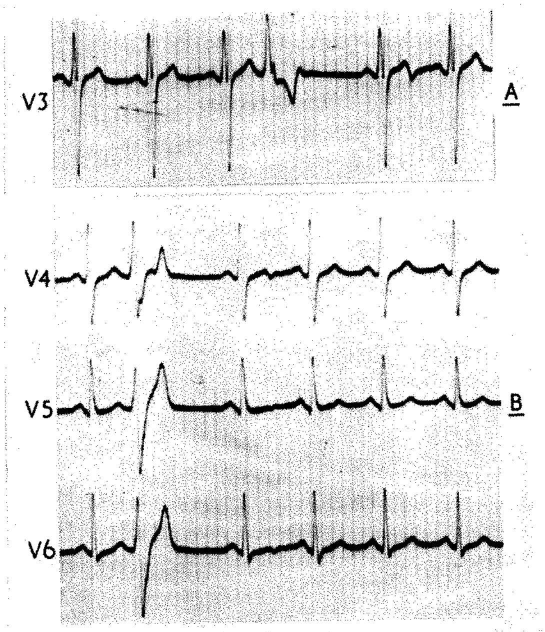

Fig. 1 *Representative changes in the T wave vector of postextrasystolic beats. The examples in this figure, as well as Fig. 2 and 3, were carefully chosen as typical of the postextrasystolic T wave changes seen, rather than the best illustrative traces. Both panels are from patients with normal baseline T waves, normal coronary arteries, and mitral prolapse.*

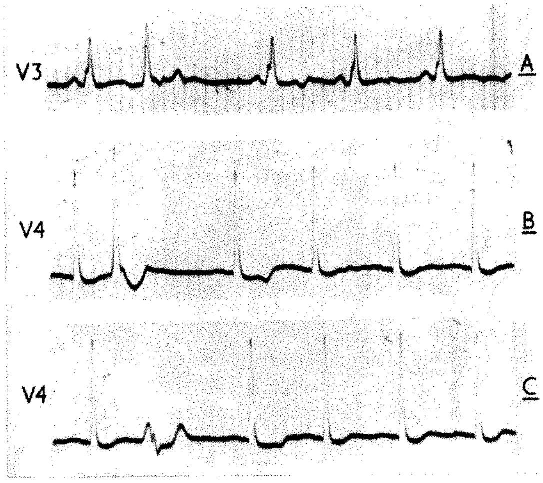

Fig. 2 *Representative changes in the T wave contour of postextrasystolic beats. Panel A is from a patient with normal coronary arteries. Panels B and C are from patients with coronary artery disease.*

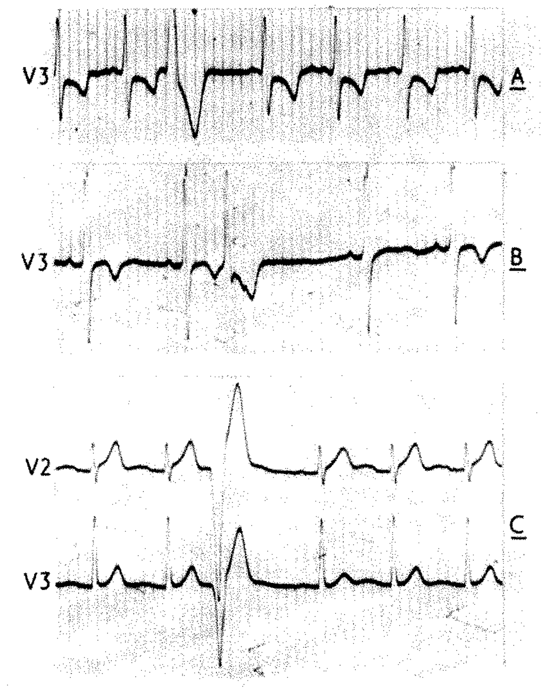

Fig. 3 *Representative changes in the T wave amplitude of postextrasystolic beats. Panels A and B are from patients with normal coronary arteries. Panel C is from a patient with coronary artery disease.*

Statistical comparisons were made with a χ^2 test. Left ventricular end-diastolic pressures and ejection fractions were compared using an unpaired t test.

Results

Thirty-six of the patients studied had significant coronary artery disease and the remaining 19 had normal coronary arteries. T changes were found in 29 (81%) patients with abnormal coronary arteries but were found as well in 13 (68%) patients with normal coronary arteries (Table). In each group, T changes were just as frequent if the resting electrocardiogram was normal or if there were baseline ST-T abnormalities. There were only 5 patients with normal baseline electrocardiograms and normal coronary arteries, but all had T changes.

T changes, when present, were most often seen in the praecordial leads (Table). T changes in leads corresponding to the distribution of major coronary arteries occurred just as frequently when the artery was normal as when the artery was significantly stenosed. In total, 47 of the arteries examined were stenosed, and 26 (55%) were associated with T changes in corresponding leads; 34 of 63 (54%) normal arteries were associated with corresponding T changes. Again, when lead groups were analysed for baseline ST-T abnormalities, no significant difference in the prevalence of T changes was observed.

Seven patients with normal coronary arteries had mitral prolapse. The presence of prolapse was not associated with a significantly increased prevalence of T changes (5 of 7 patients with prolapse had T changes while 8 of 12 normal subjects without prolapse had T changes).

Anteroapical asynergy was associated with T changes in leads I, aVL, V1 to V6 in 12 of 15 patients (80%). But even when anteroapical wall motion was normal, 75 per cent had T changes in those leads. T changes in leads II, III, and aVF were found in 5 of 21 (24%) with inferior asynergy and in 38 per cent of patients with normal inferior wall motion. Ejection fraction was in fact significantly greater ($P < 0{\cdot}05$) in patients with T changes ($0{\cdot}68 \pm 0{\cdot}02$ SEM) than in patients without such changes ($0{\cdot}58 \pm 0{\cdot}05$). Left ventricular end-diastolic pressure as well was significantly lower ($P < 0{\cdot}01$) in patients with T changes (14·0 mmHg ±0·8) than in patients without T changes (20·0 ±3·0).

Discussion

Postextrasystolic T wave changes (T changes) were first described in patients with coronary artery disease (White, 1915). Such T changes were subsequently associated with disease; with coronary obstruction (von Kapff, 1932; Levine *et al.*, 1952; Childers, 1966), with cardiac dysfunction (von Fernbach, 1934; Scherf, 1944; Ashman *et al.*, 1945; Mann and Burchell, 1954), and with ischaemia analogous to T wave changes in the stress electrocardiogram (Levine *et al.*, 1952; McLachlan, 1962). Bias was inherent in previous reports because electrocardiograms tended to be recorded more often in patients with heart disease. Moreover, only electrocardiograms of patients with spontaneous extrasystoles were used. Clinical correlations were made before the advent of angiography, and thus could not allow for precise or regional characterisation of coronary artery disease.

Dissenting reports failed to implicate T changes as diagnostic of heart disease (Fagin and Guidot, 1958; Robitaille and Phillips, 1965). Other correlates of T changes were identified, such as the inotropic state of the postextrasystolic contraction (Edmands and Bailey, 1971). T changes relate to the coupling interval of the extrasystole or the duration of the compensatory pause (Scherf, 1944; Levine *et al.*, 1952; Edmands and Bailey, 1971). However, in the absence of accurate clinical correlates, as can be obtained only by angiography, the actual significance of T changes has remained uncertain.

In this study we induced extrasystoles and therefore did not select patients on the basis of ectopy or other electrocardiographic abnormalities. T changes were found to be more frequent than previously reported, perhaps because we recorded extrasystoles in every lead. In fact, T changes were present in the majority of patients, regardless of diagnosis. The prevalence of T changes was similar if the baseline electrocardiogram was normal or if there were baseline ST-T abnormalities (either in the leads concerned or elsewhere). Since such T changes have been described as well after supraventricular extrasystoles (Scherf, 1944), and since many normal subjects have extrasystoles, T changes may, in fact, represent a frequent event.

Mann and Burchell (1954) have discussed only frank inversion of previously positive T waves. Such changes were not typical of those seen in this

Table *Prevalence of post-extrasystolic T-changes*

Coronary arteries	*N*	*Electrocardiogram*	*% Post-extrasystolic T wave changes*		
			Baseline electrocardiogram		*All patients*
			ST-T abnormal	*ST-T normal*	
LAD stenosed	22	I, aVL, V1-6	77	89	82
LAD normal	33		71	75	73
RCA stenosed	25	II, III, aVF	36	29	32
RCA normal	30		43	25	33
CAD	36	All leads	83	77	81
Normal coronaries	19		57	100	68

Abbreviations: LAD, left anterior descending; RCA, right coronary artery.

study. In addition, Scherf (1944) incriminated only T wave lowering or inversion in leads I and II. These criteria for T changes were not assessed in this study. Rather, we considered all changes in the vector, amplitude, or contour of T waves, which we felt to be more inclusive.

In this study, patients with normal coronary arteries were just as likely to have T changes (68%) as patients with angiographically shown coronary artery disease (81%). Regardless of disease elsewhere, electrocardiographic leads representing the distribution of normal coronary arteries were just as likely to show T changes (54%) as leads associated with stenotic coronary arteries (55%). Changes were most frequently seen in the praecordial leads. Levine *et al.* (1952) suggested that this occurred because of involvement of the left anterior descending artery but the results of this study show that T changes are just as frequent when the left anterior descending is normal. Therefore, T changes did not accurately assess coronary artery disease in this study.

T changes did not seem to indicate regional left ventricular asynergy. Additionally, left ventricular end-diastolic pressures and ejection fractions were similar in patients with or without T changes. Thus, myocardial dysfunction or ischaemia could not be implicated as a cause of T changes. The results of this study suggest that T changes are a manifestation of the extrasystole *per se* or the following compensatory pause and probably do not reflect cardiac status. The T changes described in this investigation (Fig. 1 to 3) cannot be used to diagnose or localise coronary artery disease.

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Serum myoglobin level as diagnostic test in patients with acute myocardial infarction[1]

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Serum myoglobin levels were measured in normal subjects and patients by means of a newly developed radioimmunoassay. Myoglobin was identified in all of 135 sera from normal adults and ranged between 6 and 85 ng/ml (mean ± SE 31 ± 1·3). Raised myoglobin levels were present in 62 of 64 patients with documented acute myocardial infarction, the mean serum concentration being 528 ± 76 ng/ml. Serial determinations in 46 patients with acute infarct showed that maximum values usually occurred within 4 hours after admission. In 19 of 42 cases, raised myoglobin levels preceded the rise in creatine kinase (CK) values; in the remaining patients, both serum myoglobin and creatine kinase were increased on admission. Only 2 of an additional 44 patients admitted with chest pain but without subsequent electrocardiographic, enzyme, or technetium-99m stannous pyrophosphate myocardial scintigraphic evidence of acute myocardial infarction had raised myoglobin levels; the mean value for this group was within the normal range (44 ± 6 ng/ml). Serum myoglobin values also were normal in patients with congestive heart failure without acute myocardial infarction, and in patients after moderate exercise and cardiac catheterisation. Transient myoglobinaemia appears to be one of the earliest laboratory abnormalities occurring in acute myocardial infarction and, therefore, should prove useful as a diagnostic aid in patients.

The diagnosis of acute myocardial infarction has been traditionally based on a characteristic clinical history and typical electrocardiographic and serum enzyme findings. However, these diagnostic tests are insufficient to establish the diagnosis in every instance. Therefore, efforts continue to be made to find additional means of documenting the presence and extent of myocardial necrosis (Wagner *et al.*, 1973; Holman *et al.*, 1974; Willerson *et al.*, 1975a). Substantial evidence suggests that damage to the cardiac muscle mass might result in release of myoglobin as well as various intracellular enzymes into the circulation. Thus, other investigators have reported that myoglobin is transiently detectable in urine or serum of some patients with acute myocardial infarction (Saranchak and Bernstein, 1974; Kagen *et al.*, 1975; Jutzy *et al.*, 1975; Kessler *et al.*, 1975). For these reasons, we have recently developed a competitive binding radioimmunoassay for myoglobin which is more sensitive than previously described methods (Stone *et al.*, 1975).

The purpose of this report is to describe the incidence, magnitude, and time course of myoglobinaemia in patients with acute myocardial infarction and to compare results in this group with those obtained in patients admitted to the hospital for chest pain but without evidence of acute infarction. In addition, we have measured serum myoglobin levels in individuals after exercise testing, cardiac catheterisation, open heart surgery, and skeletal muscle damage.

Methods

RADIOIMMUNOASSAY

Serum myoglobin levels were determined by radioimmunoassay as previously described (Stone *et al.*, 1975) except that we have recently determined that a 4-hour incubation period is adequate for sensitive and reliable determinations of serum myoglobin values using our radioimmunoassay. In brief, myoglobin isolated from human cardiac muscle ob-

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tained at necropsy was used to immunise rabbits. Antisera containing high affinity antibodies to myoglobin were employed in a radioimmunoassay procedure in which unlabelled myoglobin standards or unknown serum samples compete with ^{125}I-myoglobin for specific antibody combining sites. Separation of free from antibody-bound labelled myoglobin was accomplished by means of ammonium sulphate precipitation and the results calculated by usual methods. Standard curves were run with each assay and all determinations performed in triplicate. Values obtained in triplicate agreed with one another within 5 per cent. This system is capable of detecting 0·5 ng myoglobin and is not affected by haemolysis, lipaemia, or prolonged storage of serum at –20°C.

INDIVIDUALS STUDIED

Myoglobin levels were determined in sera from I: 135 normal adults (blood-bank donors) and II: pooled sera from 100 medical students.

The following patient groups were studied: (III) 64 patients admitted to the Coronary Care Unit (CCU) at Parkland Memorial Hospital, Dallas, Texas, for chest pain, who subsequently showed typical alterations by electrocardiogram, cardiac enzymes, and technetium–99m stannous pyrophosphate myocardial scintigraphy of acute myocardial infarction; (IV) 44 patients admitted to the CCU for chest pain but without subsequent evidence of acute myocardial infarction by the above criteria; (V) 17 patients with congestive heart failure but without recent myocardial infarction; (VI) 19 patients undergoing open heart surgery; (VII) 9 patients undergoing cardiac catheterisation; (VIII) patients exercised on the bicycle ergometer as part of a standard exercise test to evaluate the possible presence of coronary artery disease; and (IX) 5 patients with rhabdomyolysis. All sera were stored at –20°C before assay.

Results

NORMAL INDIVIDUALS (Groups I and II)

Myoglobin was identified by radioimmunoassay in all of 135 sera from normal adults and ranged between 6 and 85 ng/ml (mean ±SE 31 ±1·3 ng/ml) (Fig. 1). Pooled sera from 100 medical students yielded similar results (mean ±SE 25 ±1·2 ng/ml in 10 separate assays) and were included in each experiment. The upper limit of normal was taken as 85 ng/ml which was the highest value observed in any normal individual; this value was greater than two standard deviations from the mean.

ACUTE MYOCARDIAL INFARCTION (Group III)

Of 64 patients with documented acute myocardial infarction, 62 had raised serum myoglobin values on admission (mean ± SE 528 ±76 ng/ml) (Fig. 1). The average age of these patients was 55 years and 54 were men. Thirty patients had anterior, 27 inferior, and 7 subendocardial myocardial infarction. Forty-six patients in this acute infarction group had serial serum myoglobin levels determined every 2 hours for 36 hours after admission. Of the 46 patients studied serially, 40 had peak myoglobin levels within 4 hours after admission and 24 of these had peak levels initially. The values returned to normal within 12 hours in 6 patients and were normal in 41 per cent (19/46) of patients by 36 hours. In 42 of the 64

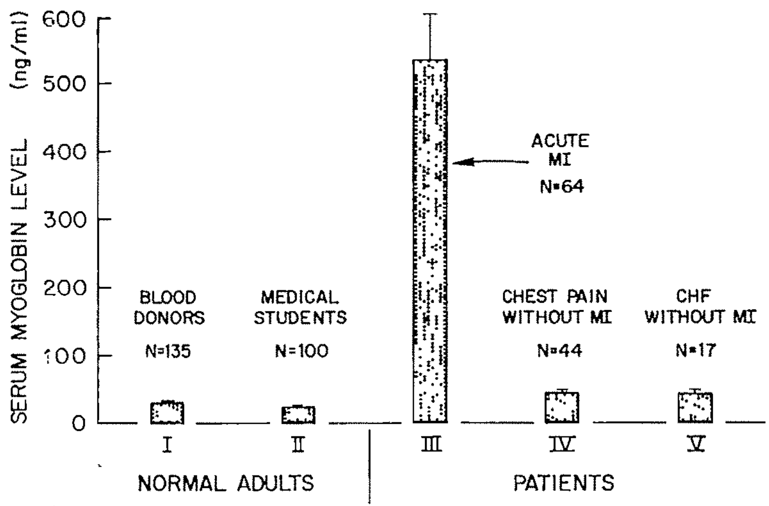

Fig. 1 *Serum myoglobin levels in normal adults and patients. The upper limit of normal was 85 ng/ml. Raised levels were found in 62 of 64 patients with acute myocardial infarction (Group III), 2 of 44 patients with chest pain but without acute infarction (group IV), and 1 of 17 patients with congestive heart failure but without acute infarction (group V). Brackets indicate standard error of the mean.*

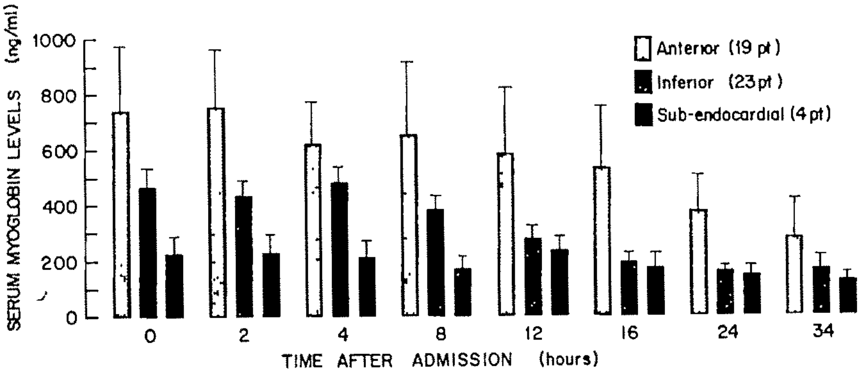

Fig. 2 *Serum myoglobin levels determined serially in 46 patients with acute myocardial infarction. Though mean values in patients with anterior infarcts were higher than those in patients with inferior or subendocardial infarctions, they were not statistically significant (P>0·05).*

patients, blood samples for total creatine kinase (CK) as well as myoglobin were obtained on admission; in 19 of these 42 the myoglobin level was raised while the CK value was within the normal range. The serum CK values in these 19 patients subsequently did rise helping to establish the diagnosis of acute myocardial infarction. In the remaining patients, both myoglobin and CK were increased on admission.

No significant difference in serum myoglobin levels was observed between patients with acute anterior, inferior, or subendocardial infarction (Fig. 2). However, in those patients studied serially, serum myoglobin levels were statistically significantly higher (Mann-Whitney U-test) (Siegel, 1956) in patients who developed congestive heart failure after acute myocardial infarction (Fig. 3).

Two patients with acute infarction did not have raised serum myoglobin levels. Since our serial studies show that peak myoglobin levels occur early and fall toward normal in many patients, it is possible that the levels in these 2 patients had returned to normal by the time serum samples were available. Alternatively, these patients may have had quantitatively small infarcts which did not result in abnormally high levels of serum myoglobin.

CHEST PAIN WITHOUT ACUTE MYOCARDIAL INFARCTION (Group IV)

In 42 of 44 patients admitted to the CCU with chest pain but who did not show subsequent electrocardiographic, enzymatic, or scintigraphic evidence of acute infarction, serum myoglobin levels on admission remained within the normal range. Serial values on specimens obtained at 2-hour intervals for 36 hours from 5 of these patients also were normal. The 2 exceptions were a patient who had digitalis toxicity with electrocardiographic abnormalities suggestive of myocardial ischaemia (140 ng/ml) and a patient admitted with ventricular tachycardia (224 ng/ml). The mean value for this group was 44±6·0 ng/ml (Fig. 1).

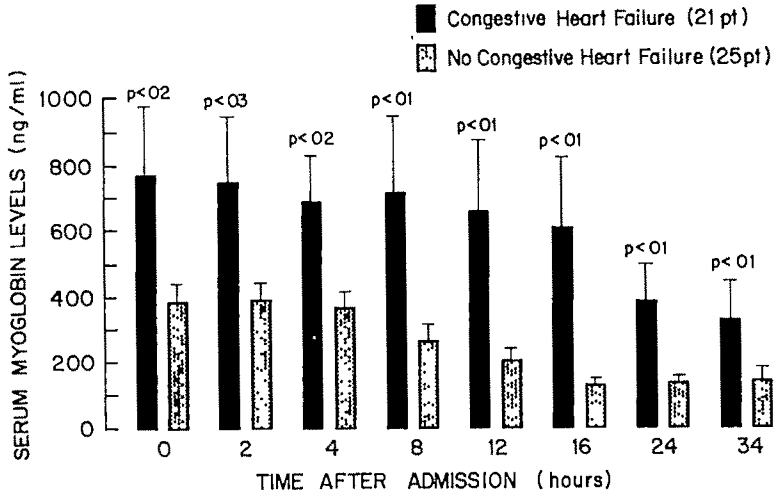

Fig. 3 *Serial serum myoglobin levels in acute infarct patients with and without congestive heart failure. The values in patients with congestive heart failure were significantly higher than those in patients without failure at each interval tested.*

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Most of these 44 patients were felt to have angina pectoris as the aetiology of their chest pain.

CONGESTIVE HEART FAILURE WITHOUT INFARCTION (Group V)
Seventeen of the non-infarct patients had clinical evidence of congestive heart failure on admission but only 1 of these (mentioned above) had a raised serum myoglobin level (Fig. 1).

OPEN HEART SURGERY (Group VI)
Nineteen patients were studied before operation and 24 hours after operation; 5 cf these patients were also studied either 5 or 12 hours after operation. Each of these patients had been on cardiopulmonary bypass and the majority of the procedures involved coronary artery revascularisation. Three of these patients were judged to have perioperative myocardial infarcts on the basis of postoperative electrocardiographic changes and technetium-99m stannous pyrophosphate myocardial scintigraphy. The preoperative myoglobin levels were normal in each patient and increased substantially during the first 24 hours after operation (Fig. 4), even in those patients without evidence of perioperative infarction.

CARDIAC CATHETERISATION (Group VII)
Nine patients undergoing left heart catheterisation with left ventricular angiography and coronary arteriography had serum myoglobin determinations performed before the procedure and at 1, 5, and 24 hours after catheterisation. The control values were normal in each patient (mean ± SE 37 ± 5·7 ng/ml) and in none of the patients was there a rise outside the normal range (>85 ng/ml) (Fig. 5).

EXERCISE STUDIES (Group VIII)
In 7 patients who underwent diagnostic bicycle exercise testing, serum myoglobin levels were obtained before and at serial intervals up to 24 hours after exercise. These patients were exercised because of chest pain suggesting coronary artery disease and they exercised to individually determined maximal levels (work load range 150–900 kilopondmetres/min, corresponding to oxygen uptakes of 0·6 to 2·1 l/min). None developed serum myoglobin levels outside the normal range; the mean values for the entire group were 31 ±2·5 ng/ml before exercise and 34 ±2·4 ng/ml after exercise.

RHABDOMYOLYSIS (Group IX)
Five patients with evidence of skeletal muscle damage were studied. None of these individuals had clinical or laboratory evidence of myocardial infarction. Serum myoglobin levels were raised in all instances (range 245–1880 ng/ml).

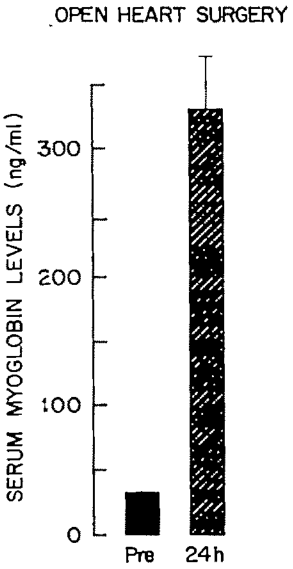

Fig. 4 *Serum myoglobin levels in 19 patients undergoing cardiac surgery. The group mean level preoperatively was 33 ±3·0 ng/ml and 329 ±39 ng/ml 24 hours postoperatively. Values in 5 of these patients studied at 5 or 12 hours postoperatively also were raised (range 166–470 ng/ml)*

Discussion

The data obtained in the present studies confirm and extend our preliminary findings using myoglobin radioimmunoassay in patients with acute myocardial infarction (Stone *et al.*, 1975). Patients with acute infarcts have serum myoglobin levels which are about ten times higher on average than those found in normal individuals. This profound rise in serum myoglobin concentration is maximal

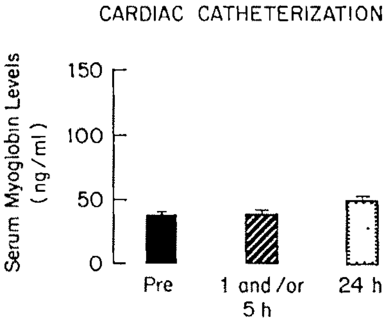

Fig. 5 *Serum myoglobin levels in 9 patients undergoing cardiac catheterisation. Values remained normal in every patient during the 24-hour interval after the procedure.*

within 4 hours after admission to the hospital in most patients and usually falls toward normal subsequently. Though it is difficult accurately to date the onset of infarction in patients, two lines of evidence strongly suggest that release of myoglobin into the circulation is an early consequence of myocardial necrosis. First, in 45 per cent of patients, the rise in serum myoglobin level preceded any rise in total serum creatine kinase. Second, in studies to be reported elsewhere we have shown that serum myoglobin levels begin to rise within 2 hours and peak in 6 hours after experimentally-induced acute myocardial infarction in awake, unsedated closed chest dogs (Willerson *et al.*, 1976).

It appears that necrosis of cardiac muscle is necessary for myoglobin release since serum levels remained normal in most patients admitted for chest pain who did not subsequently have evidence of acute myocardial infarction. It should be noted that many of these patients had chest pain of cardiac origin (angina pectoris and acute coronary insufficiency). Similarly, serum myoglobin levels were normal in 16 of 17 patients with congestive heart failure (without acute myocardial infarcts) and after moderately heavy exercise of short duration or cardiac catheterisation. Our previous studies indicated that intramuscular injections also did not raise serum myoglobin levels outside the normal range (Stone *et al.*, 1975). The consistently raised serum myoglobin levels noted in patients after open heart surgery or in subjects with rhabdomyolysis is not surprising (Kagen, 1967, 1973). Myoglobins of skeletal and cardiac muscle origin are immunochemically indistinguishable and, therefore, our radioimmunoassay is not specific for the cardiac muscle protein. Thus, a raised serum myoglobin level must be interpreted with caution and in the appropriate clinical context. Despite this limitation, the test appears valuable in the initial evaluation of patients admitted to the hospital with chest pain and a provisional diagnosis of acute myocardial infarction. Additionally, the assay should prove useful in patients in whom skeletal muscle necrosis occurs. Studies are currently in progress in this laboratory to establish this point firmly.

Various methods have been advocated as ways of assessing the extent of myocardial infarction in patients and experimental animals (Shell *et al.*, 1971; Maroko *et al.*, 1971; Willerson *et al.*, 1975b; Stokely *et al.*, 1976). The serum myoglobin level may constitute another useful measure in this regard. In dogs with acute infarction produced by proximal left anterior descending coronory artery occlusion, peak serum myoglobin levels strongly correlate with infarct size determined histologically (Willerson *et al.*, 1976). Moreover, this correlation is similar to that observed with other methods such as creatine kinase release, praecordial electrocardiographic mapping, and technetium-99m stannous pyrophosphate myocardial scintigraphy (Poliner *et al.*, 1976). Thus, serum myoglobin determined by radioimmunoassay may be useful in estimating the relative extent of infarct size as well as in its diagnosis.

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Significance of abnormal echoes in left ventricular outflow tract

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We have observed abnormal echoes in the left ventricular outflow tract in 4 patients: 3 of the subjects had bacterial endocarditis and the fourth patient had myxomatous degeneration of the aortic valve (floppy aortic valve). A single diastolic echo with fine high frequency fluttering was seen in the patient with the floppy aortic valve, whereas the patients with endocarditis had dense diastolic echoes. One of the subjects with endocarditis had associated infection of the mitral valve and an aneurysm of the anterior mitral leaflet, which was represented by dense systolic echoes on the proximal part of the mitral valve. Bacteriological cure in one of our patients resulted in the disappearance of the abnormal echoes on the aortic valve and the left ventricular outflow tract. No aortic valve destruction or abnormality was observed in a subject with endocarditis and severe aortic regurgitation; aortic regurgitation in this patient may have resulted from the presence of vegetations preventing valve closure.

The left ventricular outflow tract is represented on an M-mode echocardiogram by an echo-free space between the upper part of the interventricular septum and the anterior mitral leaflet. In normal subjects, its width is 20 to 34 mm (Gramiak and Waag, 1975). Narrowing of the left ventricular outflow tract occurs in idiopathic hypertrophic subaortic stenosis and in discrete membranous subaortic stenosis (Shah *et al.*, 1969; Popp *et al.*, 1974). The presence of echoes in the left ventricular outflow tract is an abnormal phenomenon. This report describes abnormal echoes in the outflow tract of the left ventricle in 3 patients with bacterial endocarditis and in a patient who had myxomatous degeneration of the aortic valve with aortic valve prolapse. One of the patients with bacterial endocarditis also had an aneurysm of the anterior mitral leaflet which produced an unusual echocardiographic picture.

Subjects and methods

Four patients with severe aortic regurgitation were noted to have abnormal echoes in the left ventricular outflow tract on their echocardiograms. Three patients had bacterial endocarditis and the fourth patient had myxomatous degeneration of the aortic valve. The relevant clinical data are summarised in the Table.

The first patient had vegetations on a structurally normal valve. There were no perforations or tears of the aortic valve cusps at operation. The second patient had aortic valve replacement three months after bacteriological cure of subacute bacterial endocarditis. At operation, an acutely inflamed, oedematous bicuspid aortic valve was seen; there was no aortic valve calcification. The third patient died in spite of antibiotic therapy for endocarditis. At necropsy, the aortic valve was tricuspid and was not calcified; there were vegetations on all three

Table *Clinical data*

Case No.	*Age*	*Sex*	*Infecting organism*	*Clinical course*
1	24	M	Haemolytic streptococcus	Successful operation
2	31	M	*Streptococcus viridans*	Successful operation
3	65	M	Group D streptococcus	Died
4	34	F	—	Successful operation

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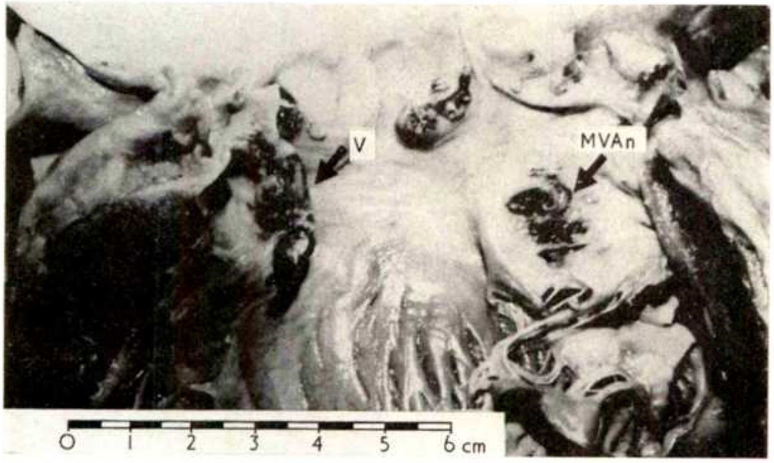

Fig. 1 *Case 3. Vegetations are seen on the aortic valve. A long vegetation (V) lies in the left ventricular outflow tract. A mitral valve aneurysm (MVAn) has formed at the site of vegetation on the anterior mitral leaflet.*

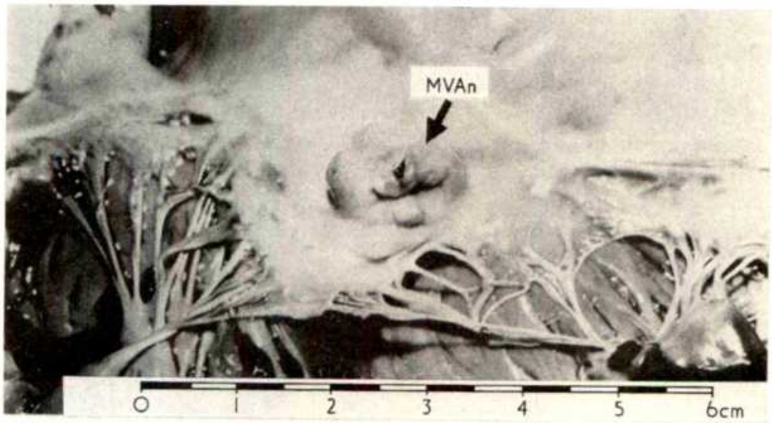

Fig 2 *Case 3. Anterior mitral leaflet showing the mitral valve aneurysm (MVAn) from the atrial surface. A small perforation is seen at the centre of the aneurysm.*

cusps (Fig. 1). A perforation of the left coronary cusp was noted and the right coronary cusp had a large vegetation which protruded into the left ventricular outflow tract. Large vegetations were found on the ventricular surface of the anterior mitral leaflet and an aneurysm with a small perforation was noted on its atrial surface (Fig. 2), this corresponded to the site of attachment of the vegetations. Histological examination of the valve at the site of the aneurysm showed inflammatory changes which suggested that this had resulted from endocarditis. The fourth patient presented with severe aortic regurgitation and obvious limitation of exercise tolerance. At operation, a redundant, floppy aortic valve which prolapsed into the left ventricular outflow tract was noted. Histological examination of the valve showed myxomatous degeneration (Fig. 3).

The patients were supine during the echocardiographic examination. An Ekoline 20 ultrasonoscope, a 10 cm focus, 0·5″, 2·25 MHz transducer, and a strip chart recorder were used. An M-mode scan from the aortic root to the left ventricle was performed on each patient.

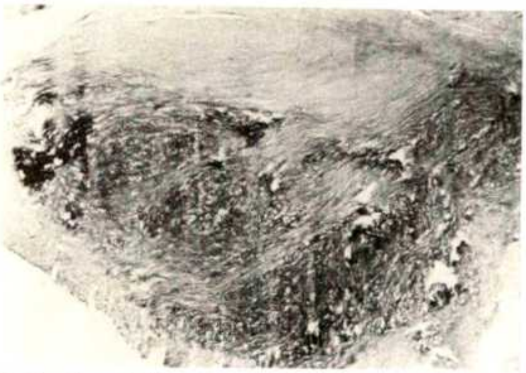

Fig. 3 *Case 4. Photomicrograph of the aortic valve. The section has been stained with Alcian blue and the dark areas represent myxomatous degeneration.*

Results

The echocardiogram of Case 1 is shown in Fig. 4. The aortic valve has a normal appearance in systole with good motion of the right and non-coronary cusp. Thick echoes are seen in diastole, which probably represent vegetations on the valve. An abnormal echo (V) is seen between the anterior mitral leaflet and the interventricular septum, i.e. in the proximal part of the left ventricular outflow tract. In the normal subject, no echoes are seen in the left ventricular outflow tract (Fig. 5). The left ventricle was enlarged and the motion of its walls was exaggerated. Fine fluttering of the anterior mitral leaflet was present.

The first echocardiogram of Case 2 (Fig. 6) was recorded during his first hospital admission, when he had physical signs of bacterial endocarditis and positive blood cultures. Abnormal thick echoes are seen in the region of the aortic valve in diastole and are probably caused by vegetations on the valve. Abnormal diastolic echoes are also present in the left ventricular outflow tract. The echocardiogram taken three months after bacteriological cure of the endocarditis is shown in Fig. 7. The abnormal echoes which were present on the aortic valve cusps and in the left ventricular outflow tract are no longer seen. The aortic valve is eccentric in diastole suggesting that the valve is bicuspid (Nanda *et al.*, 1974; Radford *et al.*, 1976).

The M-mode scan of Case 3 is depicted in Fig. 8. In systole the aortic valve cusps appear normal, whereas in diastole dense echoes are seen to fill most of the aortic root. A thick mass of echoes is also seen in the left ventricular outflow tract. Near the base of the mitral valve there are dense echoes within the substance of the valve (posterior to the echo from the vegetation) in diastole and systole

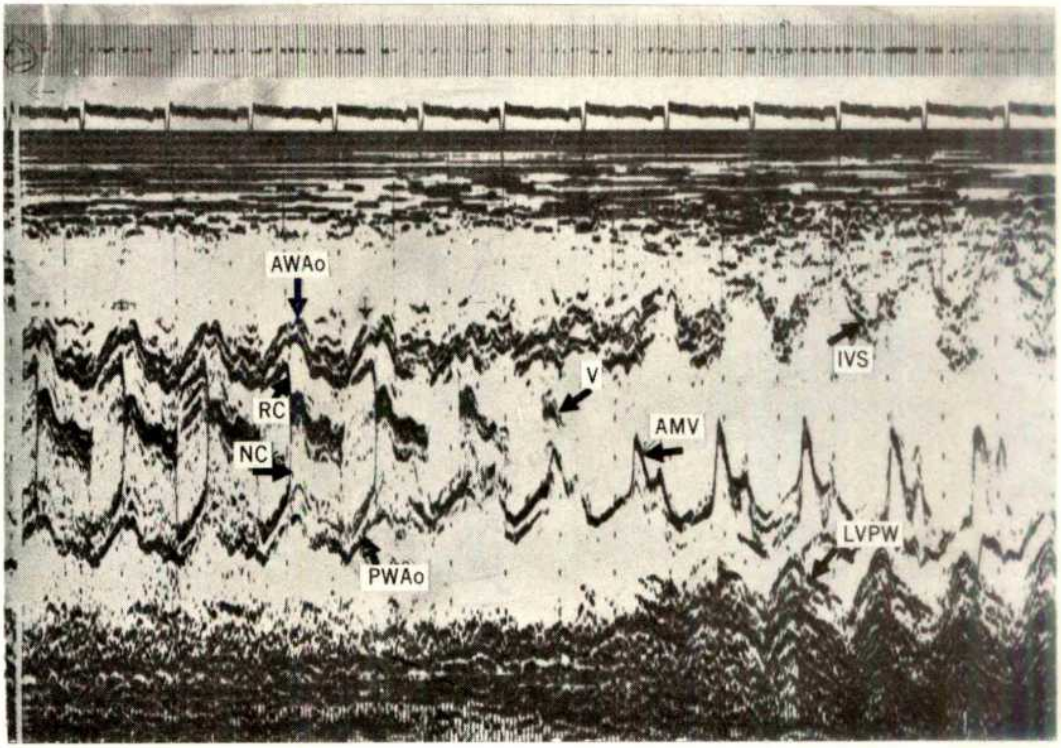

Fig. 4 *Case 1. Echocardiogram showing good motion of the aortic valve leaflets and dense echoes on the aortic valve in diastole representing vegetations. Note an echo (V) in the left ventricular outflow tract, i.e. between the anterior mitral leaflet (AMV) and the proximal part of the interventricular septum (IVS). RC, right coronary cusp; NC, non-coronary cusp; AWAo, anterior wall of aortic root; PWAo, posterior wall of aortic root; LVPW, posterior wall of left ventricle.*

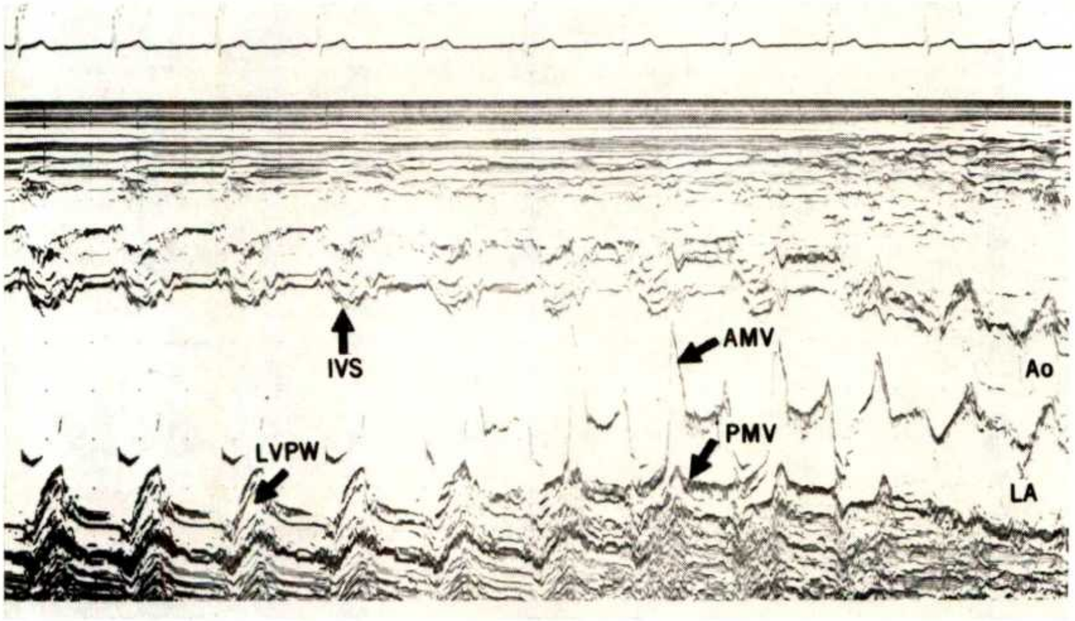

Fig. 5 *Echocardiogram from a normal athlete showing a sweep from the left ventricle to the aortic root (Ao). Note that there are no echoes between the anterior mitral leaflet (AMV) and the interventricular septum (IVS). LVPW, posterior wall left ventricle; LA, left atrium.*

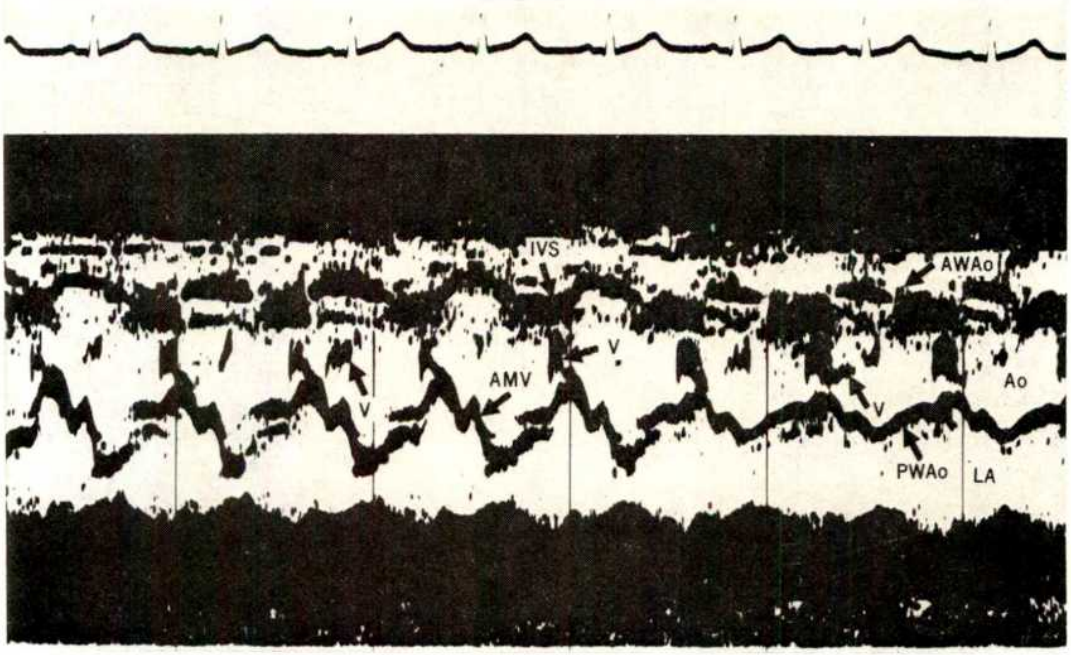

Fig. 6 *Case 2. Echocardiogram before treatment showing dense echoes in diastole in the region of the aortic valve, which probably represent vegetations (V). Similar diastolic echoes are seen in the left ventricular outflow tract, i.e. between the anterior mitral leaflet (AMV) and the interventricular septum (IVS). AWAo, anterior wall of aortic root; PWAo, posterior wall of aortic root; Ao, aortic root; LA, left atrium.*

(Fig. 9). The tip of the valve, however, shows thin linear echoes from the anterior and posterior mitral leaflets. Fluttering of the anterior mitral leaflet was present and the left ventricle was enlarged with exaggerated motion of its walls.

The M-mode scan on Case 4 (Fig. 10) shows an abnormal echo in the left ventricular outflow tract in early diastole. The aortic valve in this patient shows fine high frequency fluttering in diastole (Fig. 11). There was also fine fluttering of the anterior mitral leaflet, and an enlarged left ventricle with good wall motion.

Discussion

Dense echoes on the aortic valve in diastole suggested the diagnosis of endocarditis in our patients. The echocardiographic features of bacterial endocarditis were first described by Dillon and associates (1973) and subsequently confirmed by others (Hirschfeld and Schiller, 1974; Gottlieb *et al.*, 1974; Martinez *et al.*, 1974; De Maria *et al.*, 1975; Gramiak and Waag, 1975).

Abnormal echoes in the left ventricular outflow tract were present in all our 4 patients. Three patients had bacterial endocarditis. The fourth patient had a floppy aortic valve. In a recent review of the echocardiographic manifestations of bacterial endocarditis, Wray (1975b) observed that echoes in the left ventricular outflow tract were present in 1 case. Gramiak and Waag (1975) described another case, and Guiliani *et al.* (1975) described 8 cases of endocarditis with abnormal echoes in the left ventricular outflow tract. In one of our patients (Case 3), there was a large long vegetation hanging free in the left ventricular outflow tract at necropsy, thus confirming the echocardiographic interpretation.

The patient with aortic valve prolapse showed fine high frequency fluttering of the aortic valve in

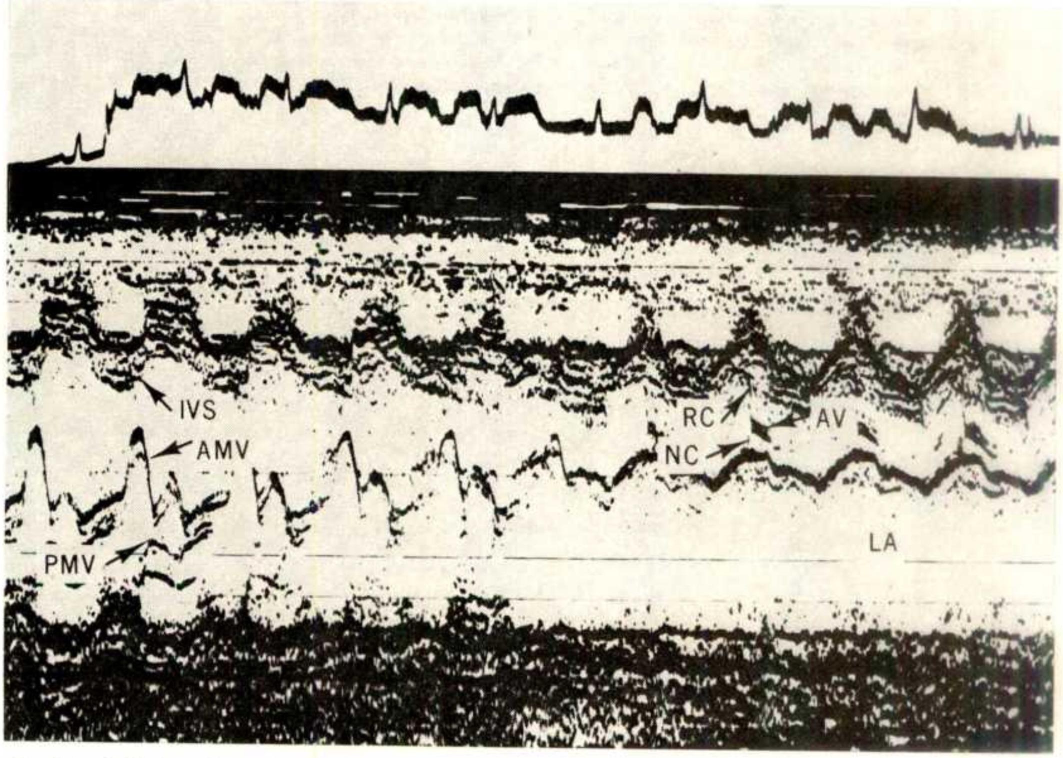

Fig. 7 *Case 2. Echocardiogram after bacteriological cure of endocarditis. The eccentric position of the aortic valve in diastole suggests a bicuspid valve. The dense echoes seen inside the aortic root and the left ventricular outflow tract on the previous tracing are no longer present. RC, right coronary cusp; NC, non-coronary cusp; AMV, anterior mitral leaflet; PMV, posterior mitral leaflet; IVS. interventricular septum; AV, aortic valve; LA, left atrium.*

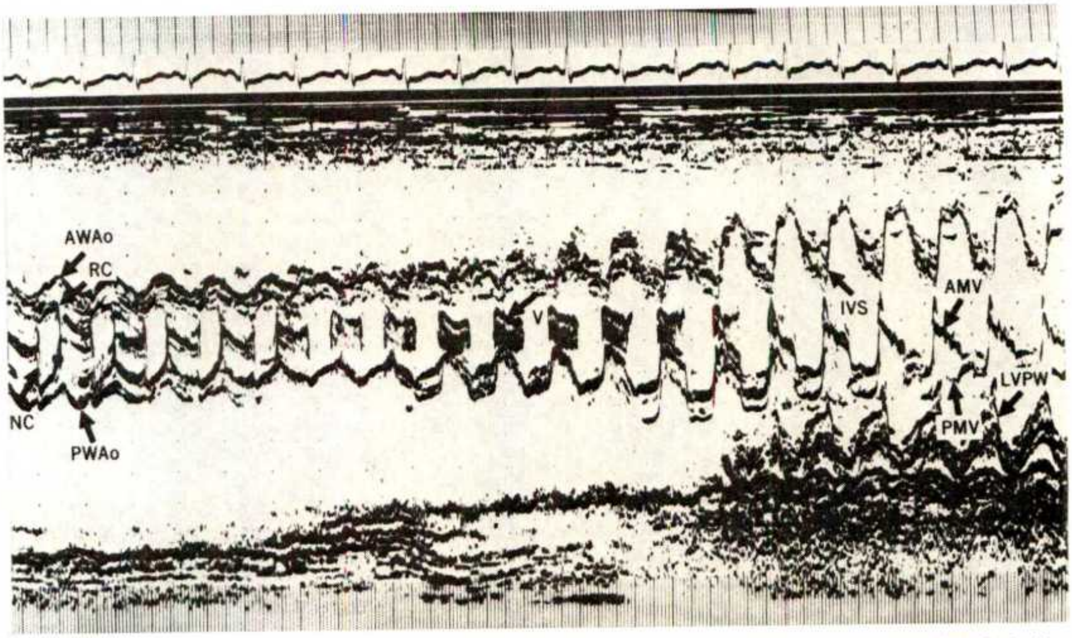

Fig. 8 *Case 3. Echocardiogram illustrating good aortic valve cusp motion in systole. Dense echoes in diastole inside the aortic root and in the left ventricular outflow tract probably represent vegetations (V). RC, right coronary cusp; NC, non-coronary cusp; AWAo, anterior wall of aortic root; PWAo, posterior wall of aortic root; AMV, anterior mitral leaflet; PMV, posterior mitral leaflet; IVS, interventricular septum; LVPW, posterior wall of left ventricle.*

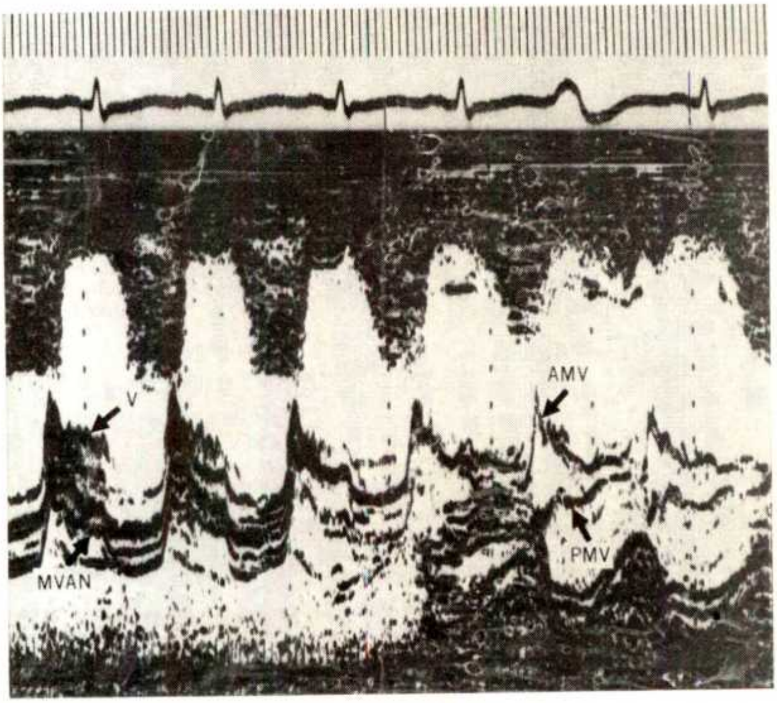

Fig. 9 *Case 3. Mitral valve echocardiogram showing the proximal part of the valve (on the left of figure) and the tip of the valve (on the right). There are multiple dense echoes in systole and diastole in the proximal part of the valve, which probably represent the area of the mitral valve aneurysm (MVAN) and vegetations (V). In contrast, the tip of the valve shows discrete single echoes arising from the anterior mitral leaflet (AMV) and the posterior leaflet (PMV).*

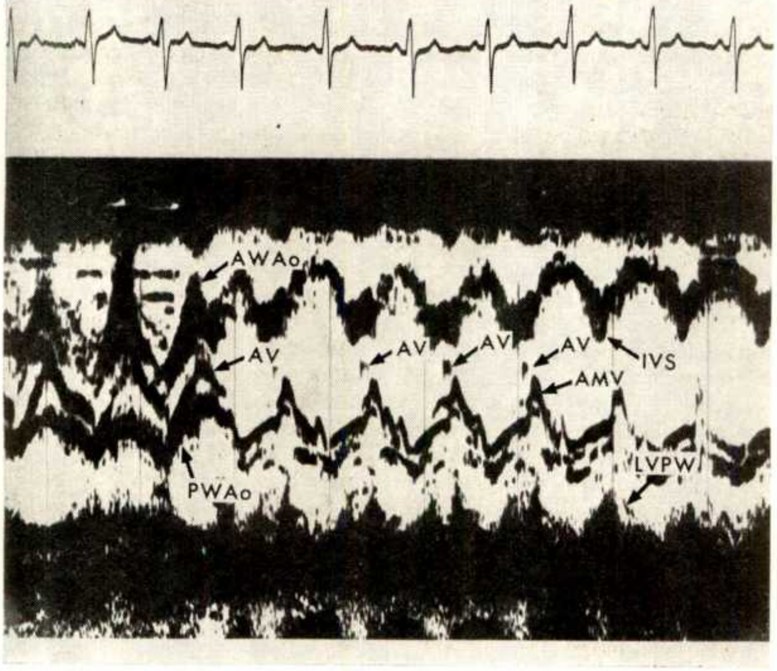

Fig. 10 *Case 4. Echocardiogram showing scan from aortic root to left ventricle. Diastolic echoes are seen in the left ventricular outflow tract, and probably arise from the floppy aortic valve which was seen at operation. AWAo, anterior wall of aortic root; PWAo, posterior wall of aortic root; AV, aortic valve; AMV, anterior mitral leaflet; IVS, interventricular septum.*

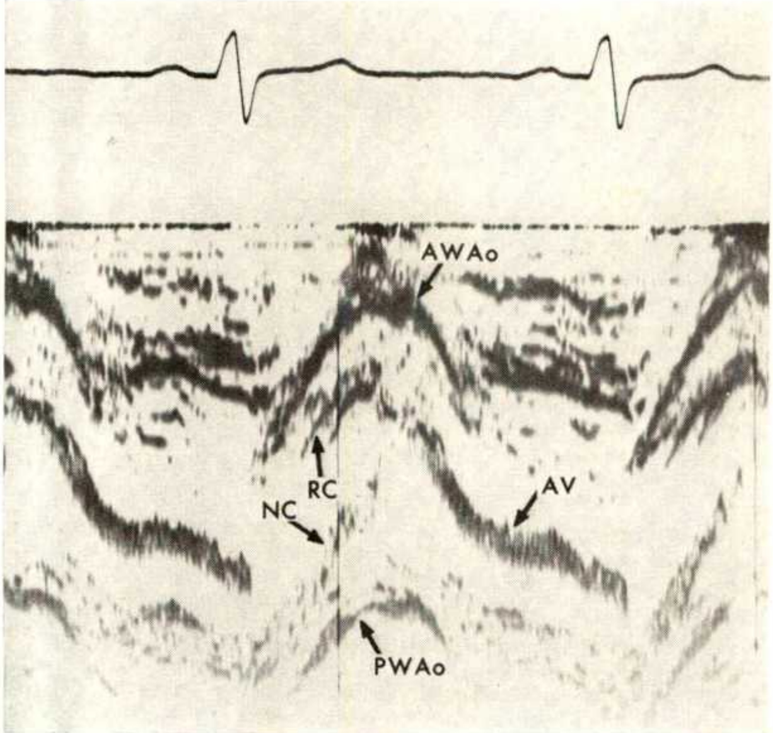

Fig. 11 *Case 4. Echocardiogram of the aortic root shows fine high frequency diastolic fluttering of the aortic valve (AV). RC, right coronary cusp; NC, non-coronary cusp; AWAo, anterior wall of aortic root; PWAo, posterior wall of aortic root.*

diastole. The patient did not have bacterial endocarditis. The abnormal echo in the left ventricular outflow tract probably arose from the aortic valve itself, which at operation was seen to prolapse. Fine diastolic fluttering of the aortic valve has been noted by us (Chandraratna *et al.,* 1975) in another patient with a floppy aortic valve. Irregular high frequency diastolic fluttering was reported in a patient with destruction of an aortic valve leaflet as a result of bacterial endocarditis (Wray, 1975a), but in this patient multiple linear diastolic echoes suggestive of endocarditis had been observed on the aortic valve one month previously. This is in contrast to the single linear diastolic echo seen in our patient with aortic valve prolapse. In our previous patient with this entity, two discrete diastolic echoes were seen which appeared to arise from the right and non-coronary cusp, respectively (Chandraratna *et al.,* 1975). High frequency diastolic fluttering of the aortic valve was also noted by Lee *et al.* (1974) in 4 patients with ruptured aortic valve leaflet; neither the aetiology of cusp rupture nor the presence of the left ventricular outflow tract echoes was mentioned in this communication. Thus, though the differential diagnosis of conditions causing abnormal echoes in the left ventricular outflow tract is difficult, the presence of a single echo or two discrete aortic valve echoes in diastole and fine high frequency diastolic fluttering of the valve are more in favour of floppy aortic valve than endocarditis. The differentiation between these two conditions is of clinical importance, because their medical management is different.

Left ventricular outflow tract echoes have also been described in a patient with discrete subaortic stenosis and in a subject with right sinus of Valsalva aneurysm (Popp *et al.,* 1974; Rothbaum *et al.,* 1974). It is unlikely that these conditions will be confused with infective endocarditis or the floppy aortic valve. In discrete subaortic stenosis narrowing of the left ventricular outflow tract, and abrupt closure of the aortic valve shortly after its opening are characteristic features (Popp *et al.,* 1969; Davis *et al.,* 1974). The patient with right sinus of Valsalva aneurysm reported by Rothbaum *et al.* (1974) had an echo in the left ventricular outflow tract which moved away from the septum in diastole and toward the septum in systole.

Case 3 also had vegetations on the ventricular aspect of the mitral valve and an aneurysm of the anterior mitral leaflet. Rodbard (1963) has pointed out that the vegetations in endocarditis of the mitral valve usually occur on its atrial aspect adjacent to the line of closure. On the other hand, infective lesions of the aortic valve occur on the ventricular aspect of the valve cusps. Thus, in this patient the primary infection was probably on the aortic valve with secondary spread to the mitral valve. Rodbard (1963) states that the high velocity regurgitant jet that occurs in aortic insufficiency may produce lesions on the chordae tendineae of the anterior mitral leaflet. In our patient, an eccentric jet caused by perforation of the left coronary cusp resulted in infective endocarditis of the anterior mitral leaflet with secondary aneurysm formation (Fig. 12). Damage to the mitral valve resulting from aortic valve endocarditis may have serious haemodynamic consequences. Acute aortic regurgitation into an uncompliant left ventricle causes a sharp increase in left ventricular end-diastolic pressure. In this situation the rapidly increasing left ventricular pressure during diastole produces premature closure of the mitral valve (Pridie *et al.,* 1971). Thus, the mean left atrial pressure may be considerably lower than the left ventricular end-diastolic pressure because there is no communication between the left atrium and the left ventricle during the latter part of diastole. However, if there were a perforation of the anterior mitral leaflet or rupture of the chordae

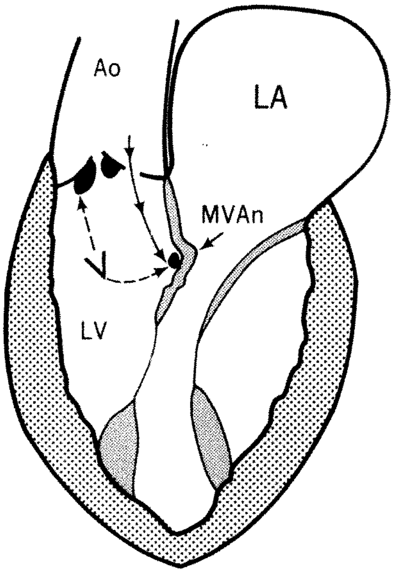

Fig. 12 *Diagrammatic section of the heart illustrating the probable mode of production of the vegetations on the mitral valve and the mitral valve aneurysm (MVAn) in Case 3. A regurgitant jet of blood through a perforation in the left coronary cusp produces local damage to the anterior mitral leaflet, predisposing to infection at that site, with secondary aneurysm formation. V, vegetations; Ao, aortic root; LA, left atrium; LV, left ventricle.*

tendineae, the left ventricular end-diastolic pressure would be transmitted to the left atrium and severe pulmonary oedema might occur. The recognition of anterior mitral leaflet involvement in patients with aortic valve endocarditis is, therefore, of considerable clinical importance. The proximal part of the valve in our patient showed dense echoes in systole and diastole whereas the distal portion was normal. The dense echoes probably arose from the vegetations and from the aneurysm of the anterior mitral leaflet. We recommend serial echocardiographic examinations of the anterior mitral leaflet in patients with aortic valve endocarditis with a view to detection of mitral valve involvement.

It is of interest that Case 1 had severe aortic regurgitation without evidence of destruction or other abnormality of the valve at operation. The large vegetations on the aortic valve of this patient probably prevented proper valve closure with resulting aortic regurgitation. We have seen a similar patient, with large non-bacterial verrucous lesions on the aortic valve (marantic endocarditis) associated with carcinoma of the pancreas, who had severe aortic reflux with a structurally normal aortic valve at necropsy. It is conceivable that in some patients with aortic valve endocarditis without valve destruction, the degree of aortic regurgitation may decrease when bacteriological cure is achieved. Interference with valve closure by vegetations may be one of the mechanisms whereby a murmur increases or decreases in intensity during the course of infective endocarditis.

Case 2 had clear-cut clinical and bacteriological evidence of bacterial endocarditis. His echocardiogram showed abnormal echoes on the aortic valve and in the left ventricular outflow tract. The record taken after bacteriological cure showed complete disappearance of these echoes, suggesting that the vegetations were no longer present. The features suggestive of a bicuspid aortic valve (eccentric position of the aortic valve in diastole) which were noted on the echocardiogram after treatment were masked by the vegetations present on the initial echocardiogram. Thus, echocardiography is helpful in the diagnosis and follow-up of the patient with endocarditis.

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Reproducibility of echocardiographic estimates of left ventricular dimensions

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Although echocardiography is ideally suited for repetitive use on a patient for evaluation of left ventricular function, the value of this application is minimised by the uncertainty as to whether changes in left ventricular dimensions observed on a patient at different times or by different observers are real or result from the ultrasonic beam penetrating the left ventricle at different angles. Accordingly, an instrument was designed and constructed in our laboratory to improve the reproducibility of echocardiographic measurements of left ventricular dimensions. The instrument represents an orthogonal reference frame by means of which the spatial orientation of the ultrasonic beam relative to the chest is determined and reproduced in subsequent studies, while the point of entrance of the beam is marked on the chest wall.

Using this instrument, left ventricular echograms were initially recorded on a group (I) of 23 subjects with or without heart disease and the study was repeated 8 hours to 49 (mean 7) days later by the same observer and also, in 16 cases, by an independent observer. The average values from 2 to 6 (mean 4) heart cycles were used for the left ventricular end-diastolic dimension (Dd), end-systolic (Ds) dimension, and their difference (ΔD). Differences in all three variables between studies were random and statistically insignificant, never exceeding 3·5 mm for Dd or Ds, and 4 mm for ΔD.

For comparison, left ventricular internal dimensions were also obtained in a separate group (II) of 14 subjects by the standard method of using the mitral valve as an internal landmark, without the benefit of this instrument. All 14 subjects had the initial study repeated within 8 hours to 11 (mean 3·8) days later by the same and also by an independent observer. Though in the group as a whole there was no significant difference in left ventricular dimensions between studies, individual variations reached 11 mm for Dd, 9 mm for Ds, and 9 mm for ΔD, and the degree of scatter was significantly larger than in group I.

This initial experience indicates that the use of this instrument improves the reproducibility and enhances the reliability of estimates of echocardiographic left ventricular dimensions and function on a patient examined at different times by the same or independent observers.

Identification of echoes originating from the endocardium of the left ventricular posterior wall and from that of the left side of the interventricular septum permits measurement of the left ventricular internal dimension throughout the cardiac cycle. Several investigators have previously validated the use of this single dimension for the noninvasive determination of the volume (Popp *et al.*, 1969; Feigenbaum *et al.*, 1970; Fortuin *et al.*, 1971; Pombo *et al.*, 1971), output (Popp and Harrison, 1970; Pombo *et al.*, 1971), and performance (Paraskos *et al.*, 1971; Pombo *et al.*, 1971; Cooper *et al.*, 1972; Fortuin *et al.*, 1972) of the left ventricle. Since it is noninvasive, echocardiography is ideally suited for repetitive use to establish changes in left ventricular size and performance as a consequence of either the natural evolution of the disease or the treatment. This application, however, is hampered by the uncertainty as to whether the changes in left ventricular dimension and function observed on a patient in serial studies carried out by the same or a different observer are real or artificial, caused by sampling from different sites of the left ventricular walls. It has been stated that the requirement of recording continuous echoes from the endocardium of the left ventricular posterior wall and of the left side of the interventricular septum, with the ultra-

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sonic transducer applied on the third or fourth left intercostal space, represents adequate constraint limiting the area of the left ventricle from which measurement of its standardised internal dimension can be made (Feigenbaum and Chang, 1972). Our experience and that of Popp *et al.* (1975), however, is that this requirement does not always ensure that the same left ventricular dimension will be recorded. Fig. 1 shows 9 left ventricular echograms obtained by one observer, from a patient in the supine position during one study period. It was possible to record echograms from the third, fourth, and fifth left interspaces parasternally. From each interspace three echograms were obtained by varying the angle of the transducer. All 9 echograms showed echoes from the endocardium of both the left side of the interventricular septum and the posterior left ventricular wall, and presented evidence of the mitral valve apparatus within the space of the left ventricle. There were distinct differences in the values obtained from different interspaces or from the same interspace at different angles, reaching 19 mm and 13 mm for the end-diastolic and the end-systolic dimension, respectively.

This report describes the results of the use of an instrument designed to improve the reproducibility of echocardiographic determination of left ventricular dimensions.

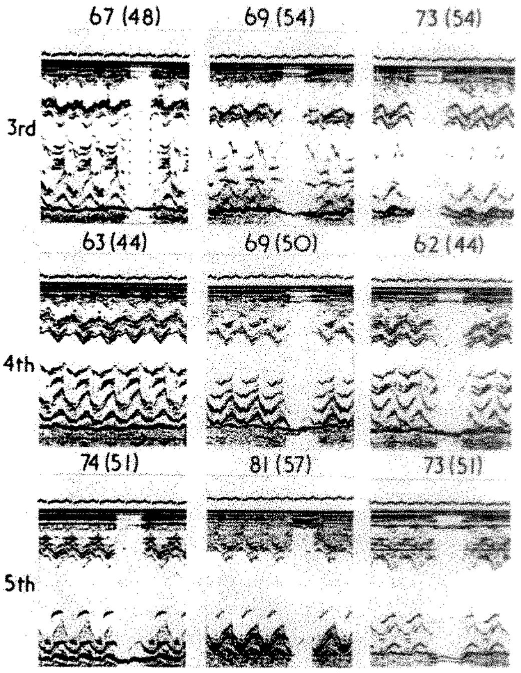

Fig. 1 *Left ventricular echograms obtained by one observer during one study period on a patient with aortic regurgitation, in the supine position. Three echograms were obtained from each of the third (upper), fourth (middle), and fifth (lower) left interspaces parasternally, by changing the direction of the ultrasound transducer. The numbers at the top of each picture represent the end-diastolic and, within parentheses, the end-systolic left ventricular dimensions. The tissue depth scale is the same in all pictures and has been retouched for clarity in the left picture of the upper row. Though the endocardium of the left side of the septum and of the posterior left ventricular wall is clearly delineated and parts of the mitral valve apparatus are represented in most of the pictures, differences in heart dimensions, even when obtained from one interspace, are marked.*

Subjects and methods

Using the instrument described below, echocardiographic studies for determination of the internal dimension of the left ventricle were conducted on a group (I) of 23 subjects (study A) and repeated 8 hours to 49 (mean 7) days later by the same observer (study B), and also in 16 cases by an independent observer (study C). Eight of these subjects had no overt heart disease. The remaining 15 subjects were patients with heart disease selected on the basis of two requirements: (1) that in all studies they were in normal sinus rhythm or sinus tachycardia and (2) that no cardiac treatment was started, discontinued, or modified in the interval between studies. Data concerning age, sex, and diagnosis of the study population are listed in Table 1.

In a separate control group (II) of 14 subjects, left ventricular echograms were obtained in the supine position using the standard method with the mitral valve as an internal landmark (study A) and repeated 8 hours to 11 (mean 3·8) days later by the same (study B) and also by a separate observer (study C). In none of these studies was the instrument used or the scanning method employed. Seven of these subjects had no overt heart disease. The remaining 7 were patients with heart disease selected on the basis of the same two requirements applied in the group I, concerning heart rate and cardiac treatment. Data on age, sex, and diagnosis of group II are listed in Table 2.

To avoid the effect of heart rate on the heart size, comparison of left ventricular dimensions in both groups between studies showing a difference in heart rate in excess of 15 per cent were omitted. Five subjects were excluded because a good quality left ventricular echogram was unobtainable in the first study. All studies on each subject were conducted at approximately the same time of the day.

A Smith Kline Ekoline 20 echograph[1] was used

Table 1 *Echocardiographic and clinical data from 23 subjects of group I*

Case No.	*Age (y) and Sex*		*Interval (d)*	*Study A*			*Study B*			*Study C*			*Diagnosis*
				HR	*Dd*	*Ds*	*HR*	*Dd*	*Ds*	*HR*	*Dd*	*Ds*	
1	32	M	2	89	63·5	54	93	60	52·5	Not done			Aortic valve prosthesis, cardiomyopathy
2	25	M	12	82	48·5	34	74	47	35·5	Not done			No heart disease
3	26	M	5	73	48·5	34	76	46·5	33	Not done			No heart disease
4	68	M	3	108	65·5	54·5	114	65·5	54	Not done			CHF, myocardial infarction
5	34	M	49	89	44·5	33·5	82	42·5	31·5	Not done			No heart disease
6	30	M	2	73	44	29·5	77	42·5	32	Not done			Hypertension, AR
7	35	F	1	95	39·5	31·5	90	38	32	Not done			Atrial septal defect
8	47	F	3	90	62	55·5	83	62	55·5	78	62·5	57·5	CHF
9	37	M*	4	123	77	68·5	107	76·5	68	100	77	69·5	Coronary artery disease, MR
10	19	M	2	68	64	45	64	67	45·5	73	65	44	AR
11	39	M	2	74	42·5	33	85	41	35	83	42·5	32·5	Angina, hypertension
12	39	M†	1	96	75	50	75	75	51	77	74·5	49·5	No heart disease
13	37	M*	18	78	49	34·5	67	52·5	34·5	64	49	32·5	AS, AR, angina, CHF
14	26	F	2	63	43·5	31	66	43·5	30	68	46·5	31	Mitral valve prosthesis, AR
15	25	M	21	66	45	32·5	67	47	31	65	46	31	No heart disease
16	24	F	3	101	41·5	27·5	100	39	27·5	102	39·5	24·5	Prolapsed mitral valve, hyperthyroidism
17	18	F	5	73	52·5	36·5	75	49	37	76	52	37·5	MR, AR
18	11	M	1/3	70	35·5	26	69	38	26·5	71	36·5	26·5	No heart disease
19	35	M	3	86	61·5	39·5	82	65	41·5	81	63·5	40	Sickle cell anaemia, MR
20	26	M	7	72	50	35	69	48	33·5	69	47	33·5	No heart disease
21	29	M	14	75	47	32	78	47	33	70	45·5	34	No heart disease
22	22	M	1	65	46·5	29	63	49·5	29·5	63	46·5	28	AR
23	39	M	2	68	52·5	38	70	53	36	67	53·5	38·5	Hypertension

Abbreviations: HR, heart rate; Dd and Ds, echocardiographic end-diastolic and end-systolic left ventricular dimension (in mm), respectively; M, male; F, female; CHF, congestive heart failure, AR: aortic regurgitation; MR, mitral regurgitation; AS, aortic stenosis. For explanation of studies A, B, and C, see text.
*Significant difference in heart rate between studies A and C.
†Significant difference in heart rate between study A, and studies B and C.

for recording the left ventricular echograms on Polaroid film or strip chart, during 'time-motion' presentation with the transducer[2] held stationary on the chest; the M-mode sector scanning technique was not used. The vertical distance between the echoes from the endocardium of the left side of the interventricular septum and from that of the left ventricular posterior wall was measured at end-diastole (Dd) defined by the R wave of the electrocardiogram, and at end-systole (Ds), defined by the peak anterior motion of left ventricular posterior wall (Fig. 2). The average values for Dd and Ds from 2 to 6 (mean 4) cardiac cycles, rounded to the nearest 0·5 mm, were used. Special care was taken to avoid bias during measurement of left ventricular dimensions on the echograms. Thus, at the completion of the project, all echograms, containing full identification data on the back, were mounted on

[1] Smith Kline Instruments, Palo Alto, California.
[2] 2·25 MHz focusing transducer (model C-14).

Table 2 *Echocardiographic and clinical data from 14 subjects of group II*

Case No.	*Age (y) and sex*		*Interval (d)*	*Study A*			*Study B*			*Study C*			*Diagnosis*
				HR	*Dd*	*Ds*	*HR*	*Dd*	*Ds*	*HR*	*Dd*	*Ds*	
1	44	M	1/3	65	60	40·5	63	54	41	65	60	41·5	Chronic renal failure, hypertension
2	13	F	3	80	45·5	28·5	83	42	28	73	49	26	No heart disease
3	26	M	7	70	45	33	80	41	27	74	41·5	28·5	No heart disease
4	27	F*	1/3	85	61·5	58·5	102	63	57·5	96	65	56·5	Hypertension, CHF
5	32	M*	7	95	45·5	31·5	76	46	34·5	82	48	35	No heart disease
6	28	M	11	55	44·5	27·5	60	45	28	60	45	26	Prolapsed mitral valve
7	20	M	2	91	55	40	103	54·5	43	99	51	37·5	No heart disease
8	23	F	1	79	50	35·5	87	53	37	90	55	35·5	Mitral regurgitation
9	36	M	1/3	69	45	28	70	55·5	36·5	66	56	36	No heart disease
10	33	M	7	61	49·5	28	57	51	34	60	55	37	No heart disease
11	23	M	7	63	42	31·5	64	45	27·5	66	45	27	No heart disease
12	16	M	3	76	60	41·5	66	64·5	41·5	66	65·5	44·5	Aortic regurgitation
13	26	M	2	84	55·5	34	82	51	37	83	47·5	31	Hyperthyroidism
14	49	F	2	113	46·5	29·5	124	43·5	29·5	119	40	24·5	Prolapsed mitral valve

Abbreviations: Same as in Table 1.
*Significant difference in heart rate between studies A and B.

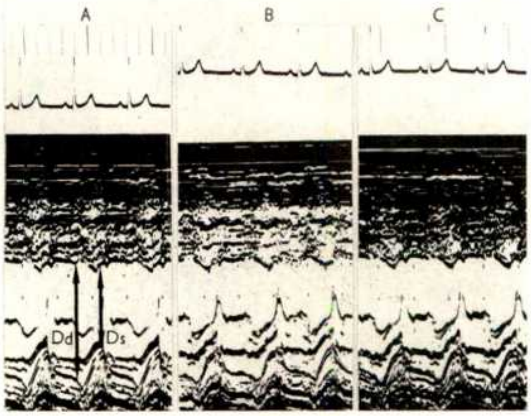

Fig. 2 *Representative echograms of the left ventricle obtained on Case 18 (see Table 1) by the first observer (A), and repeated 8 hours later by the same (B) and an independent observer (C). All three echograms were obtained by use of the instrument.*
Dd and Ds: end-diastolic and end-systolic left ventricular dimension, respectively.

non-transparent cards and randomly assigned to each of the two observers who independently carried out the measurements.

In each of the two groups, values for Dd, Ds, and ΔD from studies A and B were compared with each other and also with those obtained from study C. Statistical analysis of the results was done separately for each group, using the Student's t test for paired data. The level of statistical significance was set at $P < 0{\cdot}05$.

The instrument used in the studies of group I (Fig. 3) consists of a rectangular (89 × 193 cm) hard wooden board that has receptacles for the attachment of four metal poles supporting a rectangular (56 × 69 cm) transparent acrylic plate at a fixed height (48 cm) above the board. The surface of the plate is divided in centimetre squares so that any point on it can be identified by its co-ordinates on the X-axis (right-left) and Y-axis (head-foot). The scale of these axes is marked along the corresponding edges of the plate. A special telescopic pointer (Fig. 4), constructed in our labroatory, can be firmly attached to the back of the ultrasonic transducer and manually expanded along an imaginary extrapolation of the central longitudinal axis of the ultrasonic beam.

The board, covered by a sheet, is placed on the examining bed[1] whose surface is hard enough to prevent sagging. The subject to be examined is placed on the board with the long axis of the body parallel to that of the board, as checked by visual observation, and the head supported by a small pillow. The metal poles are screwed into place, the plate is placed on top of them, and the system is ready for use.

In the first study the transducer, with the pointer attached to it, is applied on the sternal end of the 4th or 5th left intercostal space with firm and steady pressure, and all necessary adjustments in the direction of the transducer or the gain and depth compensation controls are made until a technically satisfactory left ventricular echogram appears on the oscilloscopic screen. When the picture is about to be taken, the examined person is instructed to remain still and breathe shallowly, and an assistant manually

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[1] 'WALK-OFF' Physical Therapy Treatment Table, Laberne MFG, Columbia, S.C.

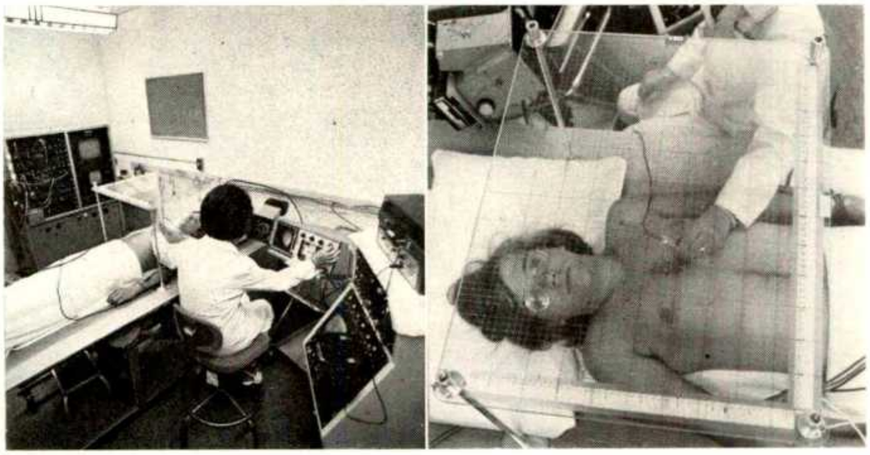

Fig. 3 *The instrument in use as seen from a distance (left); a close-up view from above (right). The echogram is about to be taken. The tip of the pointer is kept in contact with the plate by an assistant (not shown).*

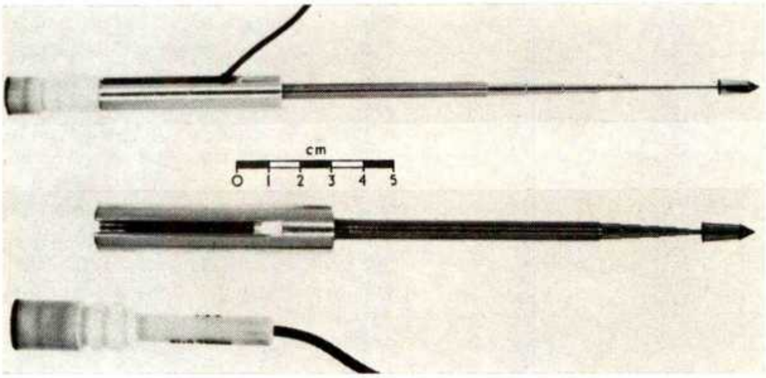

Fig. 4 *The pointer before (lower) and after its attachment on the ultrasonic transducer (upper). The metric scale shown applies to the lower half of the picture only.*

expands the pointer by exerting slow axial traction at its tip until the latter comes into contact with the plate at a point (B) (Fig. 5) which he marks on the plate. If this manoeuvre results in a deterioration of the resolution of the echogram, as observed on the screen of the echograph, this last step may have to be repeated until the wanted picture is restored by minor readjustments in the angle of the transducer. The picture is then taken at the end of a passive held expiration, and the point (C) on the anterior chest wall where the transducer was applied is marked by indelible ink for use in subsequent studies. Before the restriction on movement is removed, the transducer is placed perpendicularly[1] on and pressed against the inferior surface of the plate, and moved to a position (marked on the plate as point A) so that the tip of the expanded pointer coincides with point C marked on the chest. Finally, the co-ordinates of points A and B on the plate are noted for future use.

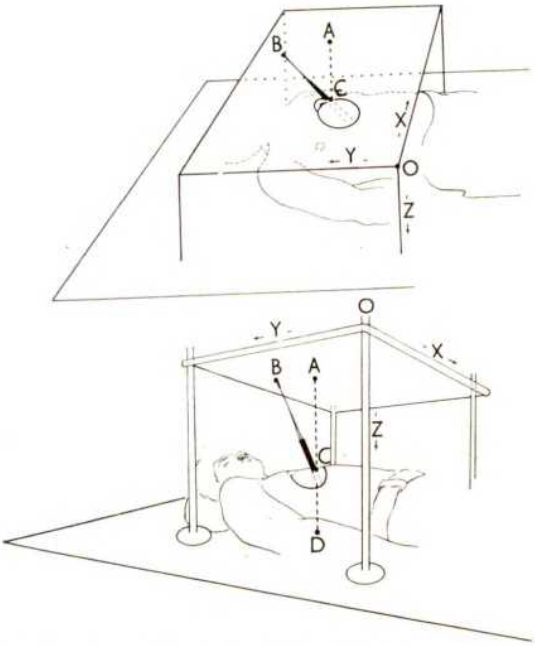

Fig. 5 *Geometric representation of the reference system employed in this study as seen from above (upper) and from below (lower). The transducer is applied at point C on the chest and the tip of the pointer is brought in contact with the plate at B. The line ACD passing through point C meets the plate (at A) and the board (at D), being perpendicular to both. The point of origin of the three axes (X, Y, Z) is at O. See text for details.*

In subsequent studies the reverse procedure is followed. First, the points A and B are marked on the plate using the co-ordinates noted from the first study. Then the subject is similarly placed on the board and suitably moved until the point C on the chest comes on the vertical line passing from point A of the plate, as checked by use of the pointer as described above. From that moment until the end of the study the examined person is instructed to remain still in order to preserve the correspondence of points A and C on the same vertical line. The transducer, with the pointer on it, is then applied on the point C on the chest and the pointer is expanded by an assistant until its tip comes into contact with the point B on the plate and held there until the echogram is recorded after suitable adjustments of gain, depth compensation, and reject control that aim at improving the clarity of the echogram.

THEORETICAL CONSIDERATIONS

Theoretical analysis of the structure and use of the presented instrument requires the following assumptions:

(1) That the central axes of the ultrasonic beam, the transducer, and the pointer lie on the same

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[1] The perpendicularity of the transducer and the plate is ensured by the requirement that the whole of the rim of the concave emitting surface of the transducer be kept in apposition with the inferior surface of the plate.

straight line, termed 'ultrasonic line'.

(2) That in a relaxed person lying supine on a horizontal unyielding surface, and at the same phase of respiration and cardiac cycle, the chest with its contents represents a 'rigid body' in the sense that the distances between any and all pairs of points in it are constant (Goldstein, 1950). Two corollaries of this assumption are (a) that the position of the heart relative to the thoracic cage is constant, and (b) that if a point (C) on the chest is perpendicularly projected on the common surface between the chest and the board at a point (D), the distance CD is constant (Fig. 5).

The following analysis is based on the principle that the position of a line relative to a 'rigid body' is completely defined if the position of each, relative to an independent reference frame, is defined.

I: Definition of position of ultrasonic line

The system composed of the board, the plate, and the connecting poles represents a reference frame (X, Y, Z) in relation to which the spatial orientation of the ultrasonic line can be adequately defined and reproduced by use of the co-ordinates of any two points (B and C) on this line (Fig. 5). Point B is completely defined by its two co-ordinates (X, Y) measured on the plate, the third co-ordinate, Z, being zero. Point C is also defined for the following reasons. Since point C (on the chest) and point A (on the plate) lie on the same vertical line (ACD), the X and Y co-ordinates of C are those of A and can be read on the plate. The third co-ordinate of point C along the Z axis is the segment AC=AD-CD; since AD (the distance between board and plate) is fixed and the segment CD is, for a given patient, constant (assumption 2b), it follows that their difference (AC) is also constant and need not be measured. Therefore, knowledge of the X and Y co-ordinates of points A and B alone defines the position of the ultrasonic line relative to the reference frame and permits its reproduction in the second and subsequent studies.

II. Definition of position of chest

The position of a three-dimensional object relative to a reference frame is defined by the co-ordinates of any three non-collinear points of this object. In the case of the chest, definition of only one of its points (C) is not an adequate condition to guarantee reproducibility of the position of the chest relative to the same reference frame. This is because, even with the point C fixed in space, the chest could still be rotated around an imaginary axis passing through point C and being parallel to (1) the X axis, (2) the Y axis, or (3) the Z axis, singly or in combination. However, the force of gravity and the presence of the board impose additional constraints limiting the degrees of freedom of movement of the chest. Thus, case 1 is obviously prevented by the presence of the board; case 2 would require determined muscular effort on behalf of the examined person to have one side of his body lifted from the board, which is not expected; and the requirement that the long axis of the body be kept parallel to that of the board prevents situation (3), unless the deviation is small enough to escape visual observation, in which case it is likely to be insignificant.

Thus, theoretically at least, the position of the chest, and (by assumption 2a) of the heart, relative to the reference frame, is reproducible. Since the position and spatial orientation of the ultrasonic line relative to the same reference frame was shown to be reproducible, it follows that the position of the ultrasonic line *relative to the heart* is also reproducible.

Results

A representative echogram is shown in Fig. 2. The results from group I are listed in detail in Table 1 and graphically depicted in Fig. 6. In this group, over a wide range of left ventricular end-diastolic dimension (35·5 to 77 mm), the differences in Dd, Ds, and ΔD between studies were statistically insignificant. Thus, comparison of studies A and B (same observer, different times) showed differences ranging from –3·5 to +3·5 (mean 0) mm for Dd; from –2 to +2·5 (mean 0) mm for Ds; and from –4 to +3·5 (mean 0) mm for ΔD. Comparison between studies B and C (different observers, same study period) identified differences ranging from –3·5 to +3 (mean –0·5) for Dd; from –3 to +2·5 (mean –0·5) mm for Ds; and from –2·5 to +4 (mean 0) mm for ΔD. Comparison between studies A and C (different observers, different times) disclosed differences ranging from –3 to +3 (mean 0) mm for Dd; from –3 to +2 (mean 0) mm for Ds; and from –3·5 to +3 (mean 0·5) mm for ΔD.

The results from group II are listed in detail in Table 2 and graphically depicted in Fig. 6. As in group I, the differences in Dd or Ds in this group (II) as a whole were statistically insignificant. Yet, despite the somewhat narrower range of end-diastolic left ventricular dimensions encountered in group II (40 to 65·5 mm), the individual variations in Dd, Ds, and ΔD observed in this group between studies and between observers were occasionally unacceptably large. Thus, in comparing studies A and B (same observer, different times) the differences ranged from –6 to +10·5 (mean 0) mm for Dd; from –6 to +8·5 (mean 1) mm for Ds; and from –7·5 to +7 (mean –1) mm for ΔD. When studies B and C

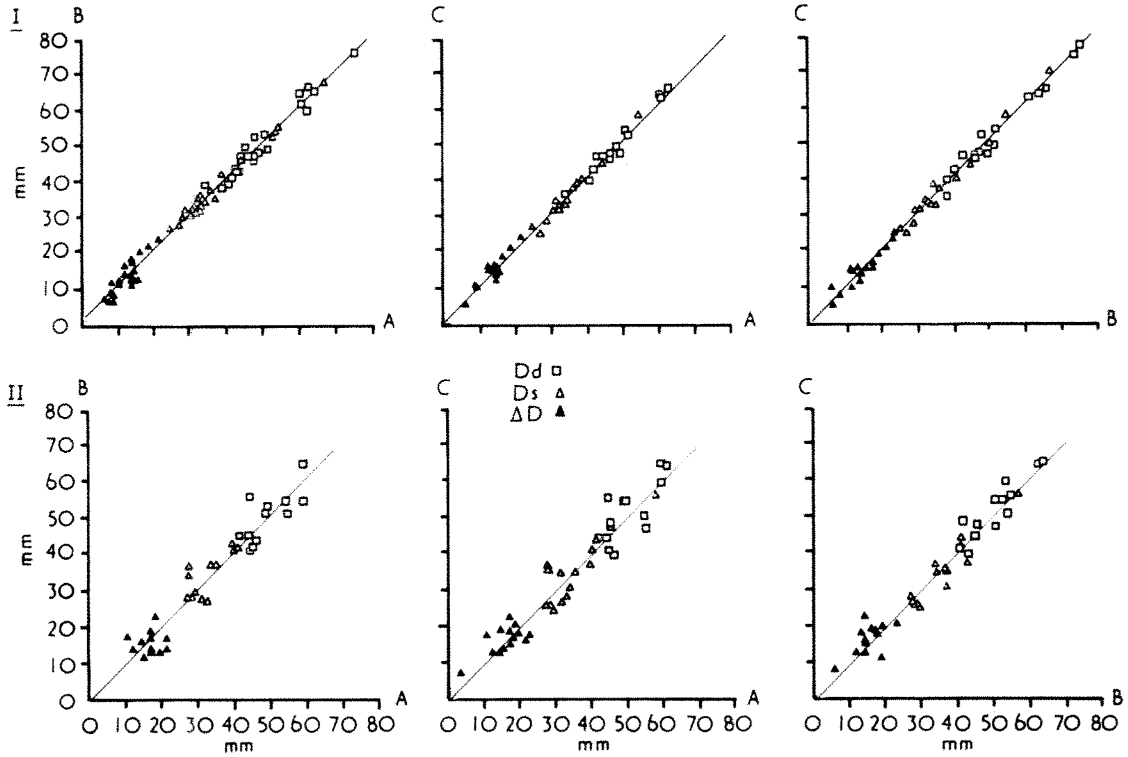

Fig. 6 *Comparison of left ventricular end-diastolic dimension (Dd, open squares), end-systolic dimension (Ds, open triangles), and their difference (ΔD, closed triangles), in group I (upper) and group II (lower). between studies A versus B (left), A versus C (middle), and B versus C (right). The lines of identity are shown. Comparisons between studies with significant difference in heart rate (see Tables) were omitted.*

were compared (different observers, same study period), the differences ranged from −3·5 to +7 (mean 1) mm for Dd; from −6 to +3 (mean −1) mm for Ds; and from −2 to +9 (mean 2[1]) mm for ΔD. Comparison between studies A and C (different observers, different times) disclosed differences ranging from −8 to +11 (mean 1·5) mm for Dd; from −5 to +9 (mean 0) for Ds; and from −5 to +7·5 (mean 1·5) mm for ΔD. These data indicate that the use of the instrument is free of any systematic bias in one direction but are not adequate to document its usefulness since—except for ΔD—such bias was also absent in the measurements made in group II where the instrument was not employed.

In order to establish the superiority of using the instrument (group I) over the old method not using it (group II), the individual differences in Dd, Ds, and ΔD noted between studies A, B, and C in group I were compared with those observed in group II, using the non-paired Student's t test for absolute differences from the mean. This test compares the degree of random variation (irrespective of direction) of individual measurements observed in one group to those obtained in the other. The results are listed in Table 3. Thus, in group II where the instrument was not used, the average differences in Dd, Ds, and ΔD between studies A and B (same observer at different times) were 1·9 to 2·7 times larger ($P < 0{\cdot}01$) than those found in similar studies in group I which had the benefit of the instrument. Similarly, the average differences between studies A and C (different observers at different times) seen in group II were 2·1 to 3·5 times larger ($P < 0{\cdot}02$) than those seen in group II. In the case of comparison between studies B and C (different observers at same study period) the average differences in Dd, Ds, and ΔD in group II were only 1·5 to 1·7 times larger than those observed in group I, the improvement being statistically insignificant for this number of observations. These data indicate that, in comparison with the old method, the use of the instru-

[1] Statistically significant difference.

Table 3 *Statistical comparison of differences in echocardiographic variables between studies A, B, and C, in two groups of subjects (I and II)*

		Comparison		
		A versus B (Same observer at different times)	*A versus C (Different observers at different times)*	*B versus C (Different observers at same study period)*
Difference in Dd:	Group I	1·82 ±0·26 ($n_1=22$)	1·27 ±0·27 ($n_1=13$)	1·56 ±0·26 ($n_1=16$)
	Group II	3·71 ±0·78 ($n_2=12$)	4·43 ±0·76 ($n_2=14$)	2·54 ±0·58 ($n_2=14$)
	P	<0·01	<0·001	NS
Difference in Ds:	Group I	1·04 ±0·16 ($n_1=22$)	1·15 ±0·23 ($n_1=13$)	1·37 ±0·23 ($n_1=16$)
	Group II	2·79 ±0·81 ($n_2=12$)	3·57 ±0·67 ($n_2=14$)	2·32 ±0·52 ($n_2=14$)
	P	<0·01	<0·05	NS
Difference in ΔD:	Group I	1·95 ±0·28 ($n_1=22$)	1·58 ±0·26 ($n_1=13$)	1·69 ±0·26 ($n_1=16$)
	Group II	3·75 ±0·67 ($n_2=12$)	3·29 ±0·58 ($n_2=14$)	2·57 ±0·60 ($n_2=14$)
	P	<0·01	<0·02	NS

n_1 and n_2 = number of subjects of group I and group II, respectively, participating in each comparison; subjects (identified in Tables 1 and 2) with significant change in heart rate between studies were excluded from respective comparison.
NS = statistically insignificant difference between group I and group II.

ment significantly improved the scatter of individual measurements of Dd, Ds, and ΔD between studies carried out at different times by the same or a different observer.

Discussion

Using estimates of one left ventricular dimension obtained by echocardiography, conclusions regarding the size, output, and performance of this chamber are drawn, and important diagnostic, therapeutic, and prognostic decisions are made. In establishing the presence and quantifying the degree of either improvement or deterioration in left ventricular performance by echocardiography, reproducibility of measurements of left ventricular dimension at different times or between observers is imperative. Left ventricular echograms can be obtained from several points of the anterior chest wall and at different angulation of the transducer, but the number of different left ventricular dimensions thus obtained is greatly restricted by the requirement of simultaneously recording continuous echoes from the endocardium of both the left ventricular posterior wall and the left side of the interventricular septum at the level of the mitral valve or the chordae tendineae which must also be represented on the same echogram. In our experience and that of Popp *et al.* (1975), in several cases more than one echocardiographic left ventricular dimension is obtainable in duplicate studies, despite adherence to this principle. Reproducibility studies have been conducted by Pombo *et al.* (1971) on a group of 11 patients in whom echocardiographic left ventricular dimensions were measured by two independent observers within an interval of 1 hour to 30 days. Though differences in left ventricular dimensions between studies were insignificant in the group as a whole, individual variations in either end-diastolic or end-systolic left ventricular dimension reached levels comparable to those observed in our group II.

The technique of M-mode sector scan (Feigenbaum and Chang, 1972) certainly represents a significant improvement since the proper left ventricular dimension may be selected out of a meridional cross-section of the left ventricle passing through the apex and the aortic valve. Certain difficulties are, however, associated with this technique. First, such complete sector scans are more difficult to obtain than single left ventricular echograms with a stationary transducer, even by experienced examiners. Second, continuous movement of the transducer during scanning may result in obtaining end-diastolic and end-systolic left ventricular dimensions from different points of the left ventricular wall. Third, this technique requires a strip-chart echocardiographic recorder, an expensive instrument not available in all laboratories. Fourth, M-mode sector scans can be obtained on a patient from more than one intercostal space with significant effects on the left ventricular dimension measured from each interspace, as recently shown by Popp *et al.* (1975). Their concept of the 'standard interspace' defined as the one that 'permits recording of the anterior mitral leaflet while the transducer is held perpendicular to the chest wall, with only slight medial but no superior or inferior angulation'—is a positive step in the effort to standardise measurements of the echocardiographic left ventricular dimension. Use of the 'standard interspace' by these investigators resulted in a small difference (0 to 4, mean 0·5 mm) in left ventricular dimensions measured on duplicate echograms carried out during the same study period on 14 patients. However, data concerning the use of this method at different times and by different observers are not available.

The instrument employed in this study is inexpensive and its use prolongs the examination only for a few minutes. Its disadvantages are that (1) it can only be used with the patient in the supine position; (2) it necessitates marking the point of application of the transducer on the chest, for use in subsequent studies; and (3) it requires the help of an assistant to expand the pointer and keep its tip in contact with the plate, during the recording of the echogram. Compared with theoretical estimates of Linhart *et al.* (1975), these data indicate that the variability of measurements obtained using this instrument on individual patients at different times and by different observers justifies its use for follow-up studies of left ventricular performance.

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Primary restrictive cardiomyopathy
Non-tropical endomyocardial fibrosis and hypereosinophilic heart disease

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Eleven patients with a restrictive cardiomyopathy are described. Seven of these had biventricular disease and in them the haemodynamic abnormality resembled that in constrictive pericarditis but the condition was distinguishable because of unequal involvement of the two ventricles, murmurs of atrioventricular valve regurgitation, or characteristic ventricular deformity on angiography. Two of these patients had eosinophilia with the clinical features of Löffler's endocarditis. In 4 patients the disease was apparently confined to the left ventricle; they were investigated on account of atypical chest pain, third heart sound, or abnormal electrocardiogram.

Simultaneous measurements of left ventricular pressure and volume throughout diastole were made in 3 patients and showed rapid but abruptly curtailed left ventricular filling. Transvenous endomyocardial biopsy in 2 patients showed fibrous tissue with collagen and irregular elastic fibrils. Surgical biopsy in 3 patients excluded pericardial constriction but was diagnostically unhelpful because of failure to obtain endocardium. Necropsy in one patient showed that the heart had features indistinguishable from tropical endomyocardial fibrosis.

It is suggested that the spectrum of ventricular abnormalities in these patients results from endomyocardial fibrosis of varying severity and probably of differing cause. This study has shown that 'tropical' endomyocardial fibrosis may occur outside the tropics and suggests that eosinophilia may play a leading role or associated part in the genesis of some cases.

The early descriptions of heart muscle disease were based on clinical likeness. As it has become possible to investigate and define ventricular function with greater precision, the name given to the heart muscle disorder has described the disturbance of ventricular function and finds its counterpart in the pathological anatomy and histopathology (Goodwin and Oakley, 1972; Oakley, 1975).

In this study, we describe a clinically recognisable group of patients who share a diastolic abnormality of a type which is not seen in patients with other primary cardiomyopathies nor in rare specific disorders such as amyloid heart disease. We wish to reintroduce the term restrictive cardiomyopathy to describe this group which includes patients with the clinical syndrome of Löffler's eosinophilic endocarditis as well as patients with angiocardiographic and necropsy findings typical of tropical endomyocardial fibrosis.

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Patients

Eleven patients were studied over a 3-year period between July 1972 and July 1975. We have not included a larger number of clinically similar patients, seen by us before or after this but not personally studied.

These were 7 men and 4 women whose ages ranged between 20 and 58 years (Table 1). Seven were white and had not lived in the tropics. The 4 exceptions were an Iranian woman (case 4), a Sudanese man (case 8), a Saudi Arabian man (case 7), and a West Indian man (case 5) who had lived in this country for most of his life.

CLINICAL FEATURES (TABLE 1)

Five of the patients (cases 1, 2, 3, 4, and 5) presented with features of predominant right heart failure with little or no cardiomegaly, resembling constrictive pericarditis. Case 1 with atypical chest

Table 1 *Clinical, radiographic, and electrocardiographic data*

Case No.	*Sex and age (y)*	*Duration of symptoms (y)*	*Presenting symptoms*	*Clinical signs*							
				JVP	*Rhythm*	*S3*	*S4*	*Murmurs*	*Oedema*	*Ascites*	*Hepatom*
1	F 46	8	Atypical chest pain; recent effort dyspnoea	+ +	SR with intermittent atrial arrhythmias	+	0	0	+	0	+
2	F 35	1	Abdominal swelling	+ + +	SR	+	0	Soft apical systolic murmur	0	+ + +	+ +
3	F 45	1	Dyspnoea and oedema; vague chest pain	+ + +	SR	+	+	0	+	+	+ +
4	F 37	2	Dyspnoea; oedema	+ +	SR	+	0	0	+	+	+ +
5	M 32	1	Intermittent claudication	+ +	SR	+	0	Soft systolic murmur over apex and left sternal edge	0	0	+
6	M 35	2	Fever, weight loss, malaise, dry cough, rash, dyspnoea	+ +	SR	+	0	Murmur of mild mitral regurgitation	0	0	+
7	M 20	1	Effort dyspnoea: tiredness; weakness in legs	+ +	SR	+	0	Murmur of tricuspid regurgitation	0	0	+ +
8	M 36	—	Asymptomatic	N	SR	+	0	0	0	0	0
9	M 32	9/12	Atypical chest pain	N	SR	+	+	Soft apical systolic murmur	0	0	0
10	M 43	1/12	History suggestive of preinfarction angina	N	SR	+	+	0	0	0	0
11	M 58	3/12	Atypical chest pain	N	SR	+	0	0	0	0	0

JVP, jugular venous pressure; S3, third sound; S4, fourth sound; SR, sinus rhythm; LA, left atrium; RA, right atrium; N, normal.
*Normal eosinophil count: less than 0·55 × 10^9/l.

pain was found on examination to have signs of right heart failure. Case 5 presented with bilateral intermittent claudication and was subsequently found to have a cardiac abnormality with a raised venous pressure and an abnormal electrocardiogram. Cases 6 and 7 presented with a constitutional illness, with fever, weight loss, cough, and biventricular heart failure, and had eosinophilia. Four of the patients (cases 1, 9, 10, and 11) were referred because of chest pain which had been thought by their doctors to be angina; if it had not been for this pain, they would probably not have been referred. Case 8 was asymptomatic, but evidence of cardiac abnormality had been found when he was seen at another hospital for an unrelated complaint.

The most prominent physical sign was a third heart sound and this was present in every case. The third heart sounds were loud and early, between 0·08 and 0·12 s after aortic valve closure. Two patients (cases 2 and 3) showed asynchronous right and left ventricular third heart sounds on phonocardiography (Fig. 1) but these were not recognisable clinically. In all the patients except cases 2 and 5, the third heart sound was best heard at the cardiac apex, rather than at the left sternal edge as in constrictive pericarditis. Sinus rhythm was present in all except one patient (case 1) who had changing atrial arrhythmias including atrial tachycardia, flutter, and fibrillation. The jugular venous pressure was raised in 7 out of the 11 patients who also had non-pulsatile liver enlargement. The exceptions were the 3 patients who presented with chest pain

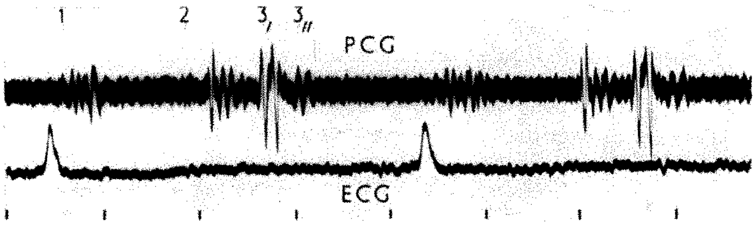

Fig. 1 *Case 2. Phonocardiogram (PLG) showing asynchronous third heart sounds.*

Chest x-ray film	*Electrocardiogram*	*Eosinophil count**
Slight cardiomegaly; LA + ; pulmonary venous congestion	Normal apart from rhythm	N
Slight cardiomegaly	Biatrial hypertrophy; lateral repolarisation changes	N
Slight cardiomegaly; pulmonary venous congestion	Left anterior hemiblock; biatrial hypertrophy	N
Slight cardiomegaly	LA + ; lateral repolarisation changes	N
Slight cardiomegaly	RA + ; right axis deviation; inverted TV4 to V6	N
Normal	LA + ; inferolateral repolarisation changes	$5{\cdot}2 \times 10^9$/l
Slight cardiomegaly; pulmonary venous congestion	Right axis deviation; LA + ; lateral T wave inversion	$7{\cdot}4 \times 10^9$/l
Normal	Inferolateral T wave inversion	N
Normal	Non-specific LV + ; lateral repolarisation changes	N
Normal	Occasional ventricular extrasystoles; repolarisation changes V3 to V6	N
Normal	Normal	N

(cases 9, 10, and 11) and the asymptomatic patient (case 8). The venous pulse showed equal *a* and *v* waves with a wide excursion and prominent *x* and *y* descents. The most prominent *y* descent was seen in case 6 who had evidence of severe right ventricular restriction from eosinophilic endocarditis (see Fig. 12). The heart was clinically enlarged in only one patient (case 7). One patient (case 2) had a wholly diastolic impulse as is sometimes felt in constrictive pericarditis. Four patients (cases 2, 5, 6, and 9) had soft late systolic murmurs of mild mitral regurgitation while case 7 had a murmur of tricuspid regurgitation.

ELECTROCARDIOGRAM

The electrocardiogram showed non-specific, nonfocal abnormalities, with a normal axis and QRS complex, in all except 3 patients. One showed left axis deviation (case 3) and 2 had right axis deviation (cases 5 and 7); the other patients all showed high normal voltages and left ventricular dominance. Repolarisation abnormalities of the ST segments and T waves were seen in 7 patients. Evidence of left atrial enlargement was present in 3, right atrial enlargement in 1, and biatrial hypertrophy in 2.

CHEST RADIOGRAPH

In 5 patients the chest radiographs were normal. The others showed slight cardiac enlargement or an abnormality in cardiac silhouette caused by left atrial or biatrial dilatation. This atrial dilatation was most pronounced in case 1, the patient with changing atrial rhythms. Evidence of pulmonary venous congestion was seen in only 3 patients. No intracardiac calcification was visible. In case 2, chest radiographs 5 years before admission to hospital in heart failure showed a normal sized heart; subsequent serial films showed progressive cardiomegaly and pulmonary venous congestion (Fig. 2).

Methods

NON-INVASIVE STUDIES

The phonocardiogram, an electrocardiographic lead, apex cardiogram, and mitral echocardiogram were recorded simultaneously, using a 6-channel Cambridge Scientific Instruments recorder (Type 72112) at a paper speed of 100 mm/s. Phonocardiograms were obtained using a suction microphone (Type 72352), and apex cardiogram tracings were obtained with a hand-held polythene funnel connected to a piezoelectric transducer with a pulse amplifier of time constant 1·6 s and a frequency response of ±3dB, 0·1 Hz to 100 Hz. Mitral echograms were obtained using the Smith Kline Ekoline 20 ultrasonoscope connected to a Cambridge recorder using both polaroid photography and strip chart recording.

HAEMODYNAMIC AND ANGIOCARDIOGRAPHIC STUDIES

The patients were premedicated with diazepam 10 mg intramuscularly. Under local anaesthetic, routine right and left heart catheterisation was carried out from the right antecubital vein, and from the femoral artery by the Seldinger method. Pressures were recorded using a Statham pressure transducer (P23Gb) and an Electronics for Medicine multiple channel recorder. Zero pressure was taken at the point midway between the plane of the catheterisation table and the sternum. Left ventricular cineangiography in the right anterior oblique position was carried out in all patients except cases 4 and 7. In 3 patients (cases 9, 10, and 11), simultaneous high fidelity measurements of left ventricular pressure and volume during diastole were carried out by a method previously described (Chew *et al.*, 1975). Left ventricular volumes were calculated by the area length method of Kasser and Kennedy (1969). Simultaneous pressures and volumes throughout diastole were plotted for each

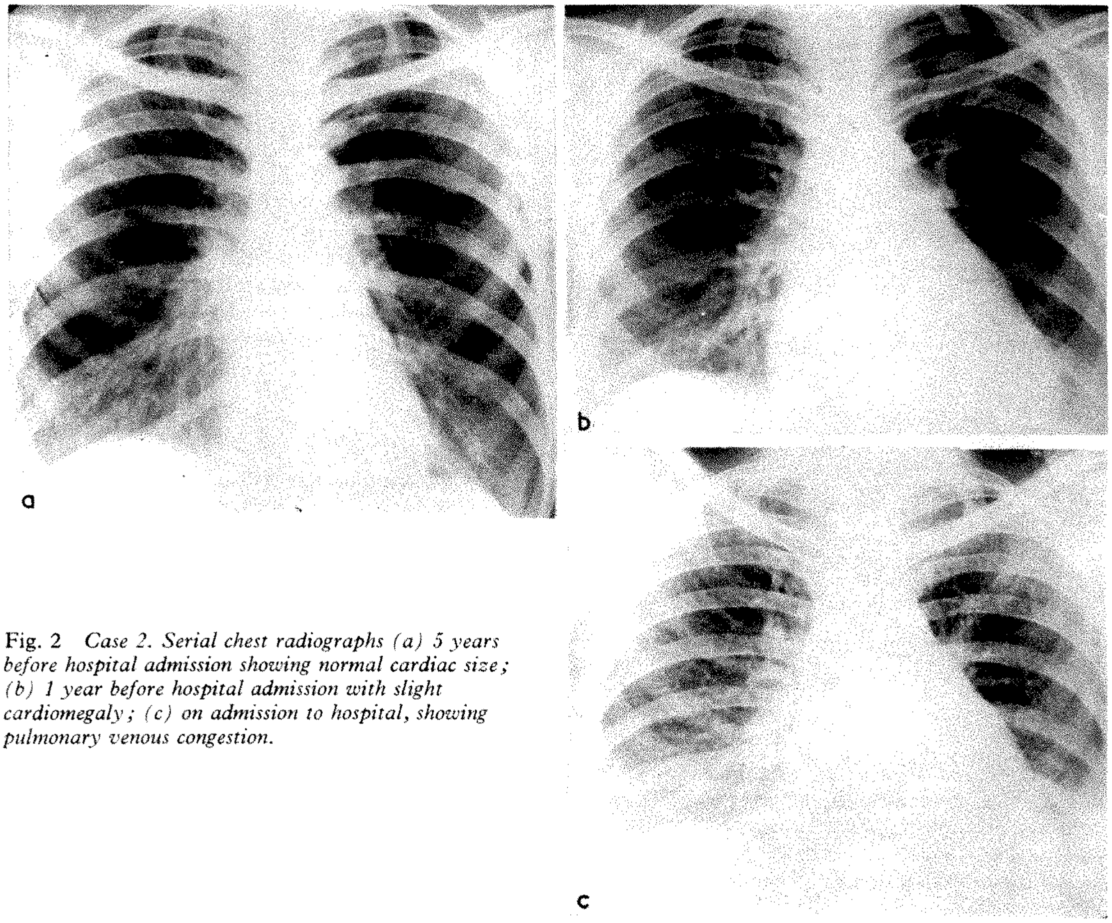

Fig. 2 *Case 2. Serial chest radiographs (a) 5 years before hospital admission showing normal cardiac size; (b) 1 year before hospital admission with slight cardiomegaly; (c) on admission to hospital, showing pulmonary venous congestion.*

patient using an Olivetti computer aided system for volume measurement. Coronary arteriography was carried out in 5 patients and transvenous right ventricular endomyocardial biopsy in 2 (cases 6 and 11).

Results

NON-INVASIVE STUDIES

The third heart sound was seen on the phonocardiogram in all the patients between 80 to 120ms after aortic valve closure, and corresponded well to the peak of the rapid filling wave on the apex cardiogram (Fig. 3).

Echocardiography showed that the diastolic closure rate of the anterior leaflet of the mitral valve was rapid (greater than 200 mm/s) in 7 of the patients while in the others the closure rates were within the normal range. Left ventricular dimensions were within normal limits and filling was rapid as reflected by the rapid early outward movements of the posterior wall echoes, best seen in case 6 (Fig. 4).

HAEMODYNAMIC AND ANGIOCARDIOGRAPHIC STUDIES (TABLE 2)

(a) *Biventricular disease (cases 1 to 7)*

The filling pressures in both ventricles were raised and except in cases 5 and 6, the left ventricular end-diastolic pressures exceeded the right ventricular end-diastolic pressures by more than 12 mmHg (Fig. 5). The left ventricular end-diastolic pressures ranged between 14 and 36 mmHg and the early diastolic pressures between 2 and 7 mmHg. The pressure record showed an early dip to normal followed by a steep early diastolic rise to a plateau which preceded and obliterated the *a* wave in 5 of the patients. In cases 1, 3, 4, and 7, the pulmonary

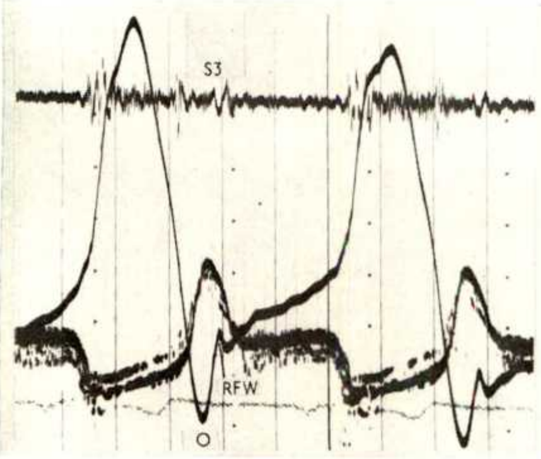

Fig. 3 *Case 3. Simultaneous phonocardiogram, echocardiogram, and apex cardiogram showing third heart sound (S3) corresponding to peak of rapid filling wave.*

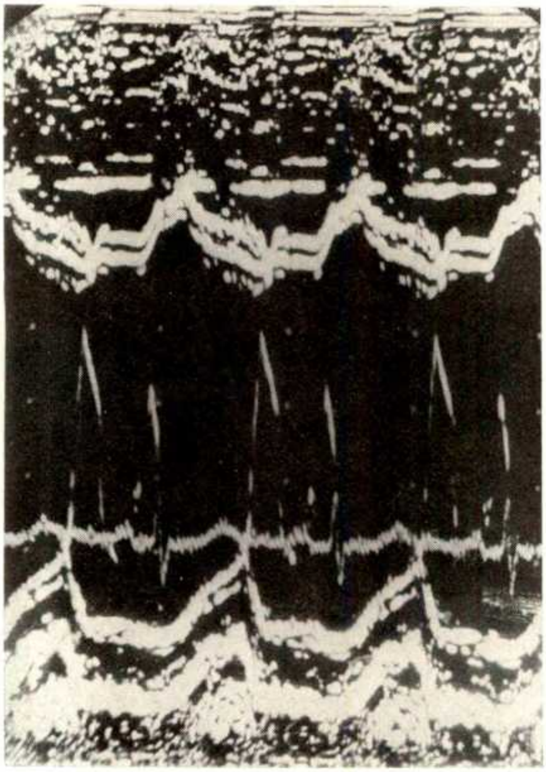

Fig. 4 *Case 6. Echocardiogram showing rapid diastolic closure rate of anterior leaflet of mitral valve, normal ventricular dimensions, and rapid outward movement of posterior ventricular wall.*

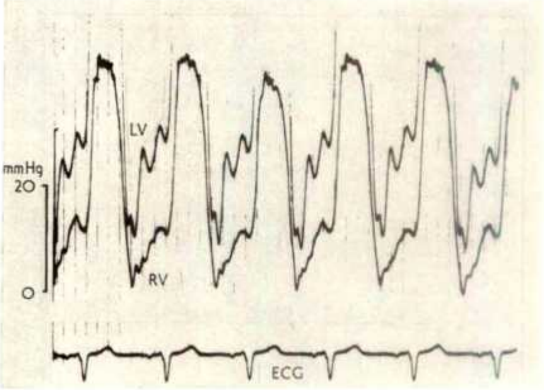

Fig. 5 *Case 3. Biventricular endocardial disease showing unequal left and right ventricular diastolic pressures.*

artery pressure was raised. The mean pulmonary artery pressure for the group ranged from 18 to 38 mmHg.

Left ventriculography showed a vigorously contracting ventricle with a smooth featureless appearance most obvious in case 2 (Fig. 6), in whom there was slight mitral regurgitation. In case 5, an unusual apical filling defect suggestive of an intraventricular tumour was seen (Fig. 7b and c). In case 6, the left ventricle appeared deformed with a small apical filling defect, but systolic contraction was normal (Fig. 8c and d). Ejection fractions were normal in 3 cases. Case 4 was studied in Iran by Dr. Rashid Massumi and systolic function as judged ventriculographically was reported as normal. Volumes were not calculated in case 6 because of persistent coupled ventricular ectopic beats during ventriculography.

Right ventriculography in cases 5, 6, and 7 showed obliteration of the apex of the right ventricle, exaggerated contraction of the infundibulum, and tricuspid regurgitation (Fig. 7a, 8a and b).

(b) *Left ventricular dysfunction only (cases 8 to 11)*
The right heart pressures were normal. The left ventricular end-diastolic pressures were invariably raised (ranging from 18 to 32 mmHg) while the early diastolic pressures were normal; the left ventricular pressure records showed a 'dip and plateau' appearance (Fig. 9).

Left ventriculography in these cases showed normal ventricular configuration and contraction. In 2 cases, there was diminished trabeculation and papillary muscle indentation giving a smooth outline to the left ventricular cavity. Ejection fractions were normal.

Coronary angiograms in cases 9, 10, and 11 were normal.

Table 2 *Haemodynamic, angiographic, and pathological data*

Case No.	Pressure (mmHg)						LV volume		CI (Fick) (l/min per m²)	Ventriculographic appearance	Coronary angiogram	Pathological examination
	RA (mean)	PAW (mean)	PA (mean)	RV (s/end-d)	Left ventricle		EDV (ml)	EF (%)				
					s/early-d	End-d						
1	14	24	30	45/14	130/7	30	46	74	1·6	Normal LV size; smooth ventricle with good contraction	Normal	—
2	16	25	28	35/13	135/2	27	63	82	2·5	Smooth featureless LV with vigorous contraction; some mitral regurgitation	—	Thoracotomy: normal pericardium necropsy: see Fig. 10
3	13	30	35	46/17	125/4	30	78	87	2·3	Normal contraction; no mitral regurgitation	Normal	Thoracotomy: no pericardial thickening
4	15	25	34	53/21	104/4	36	*	*	1·9	(Normal)*	–	Thoracotomy: normal pericardium
5	12	10	18	20/16	110/2	14	—	—	2·3	RV angio: small RV with apical filling defect LV angio: apical filling defect	—	Exploratory cardiotomy: small LV with fibrous mass in lower part of septum
6	23	20	23	35/19	110/3	24	†	†	2·0	RV angio: large apical filling defect LV angio: apical filling defect	—	RV endocardial biopsy: endocardial thickening with collagen and irregular elastic fibrils; no eosinophils
7	16	32	38	53/16	100/6	35	—	—	2·1	Dilated RV with apical filling defect	—	—
8	8	15	18	32/13	140/2	18	86	80	2·2	Undilated LV with good contraction; no mitral regurgitation	—	—
9	6	10	15	22/7	145/5	18	73	82	2·6	Slight LV hypertrophy with good contraction; reduced trabeculation	Normal	—
10	5	14	18	20/8	120/8	20	42	72	2·7	Normal LV shape and contraction	Normal	—
11	6	20	24	28/10	170/4	32	66	77	1·9	Normal LV appearance	Normal	RV endomyocardial biopsy: excess fibrous tissue; no amyloid

RA, right atrium; PA, pulmonary artery; PAW, pulmonary artery wedge; RV, LV, right and left ventricle; s, d, systolic and diastolic; EDV end-diastolic volume; EF, ejection fraction; CI, cardiac index.

*Left ventricular angiogram done in Iran and reported as normal.

†Not calculated because of persistent coupling.

HISTOPATHOLOGY

In cases 2, 3, and 4, exploratory thoracotomy and surgical biopsy were carried out. The pericardium was normal and the left ventricle small and thick-walled in each patient. Histological examination of the myocardium showed no special features apart from an increase in interstitial fibrous tissue and some hypertrophy of myocardial fibres.

Case 2 died two years after her initial illness, following operation for resection of gangrenous small bowel resulting from volvulus around band adhesions. The heart weighed 460 g (normal 300 g). Both ventricles were mildly hypertrophied but the most striking abnormality was the grossly thickened endocardium which measured up to 6 mm in some areas (Fig. 10). This endocardial thickening involved the apex and body of the right ventricular cavity and the inflow portion and apex of the left ventricle; the endocardial thickening stopped abruptly with a rolled edge at the junction of the

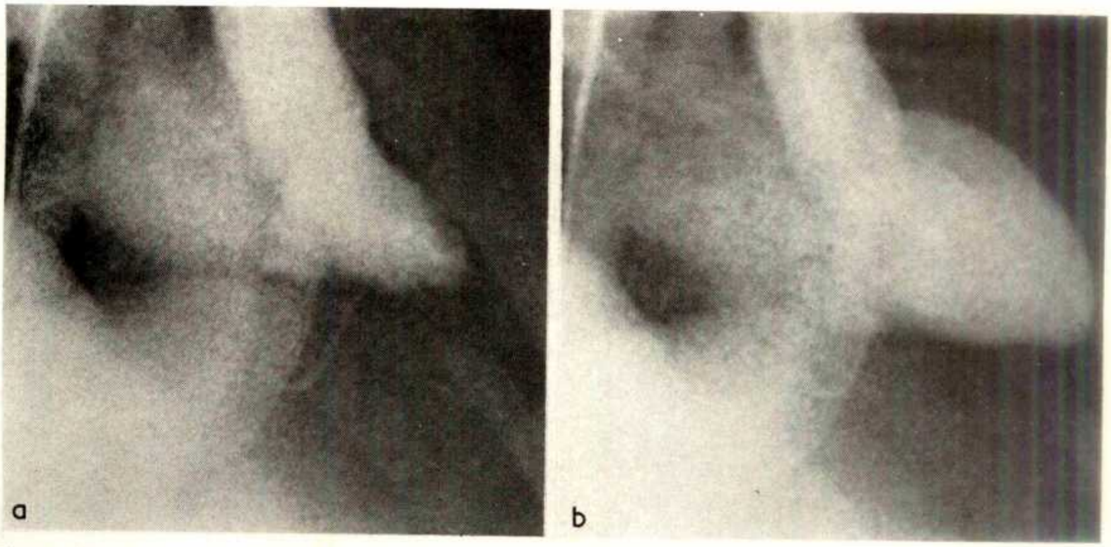

Fig. 6 *Case 2. Left ventriculogram (a) end-systole; (b) end-diastole. Smooth, featureless, well-contracting ventricle, with mild mitral regurgitation.*

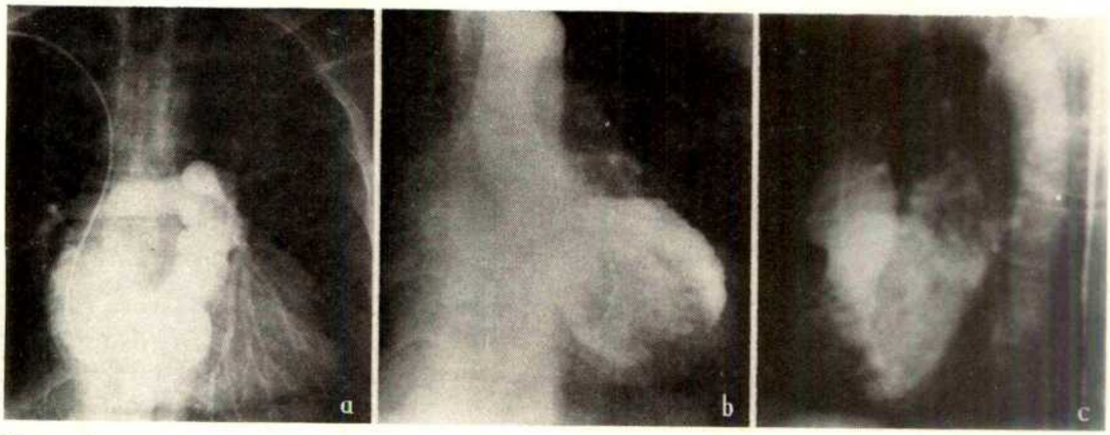

Fig. 7 *Case 5. (a) Right ventriculogram showing apical filling defect; (b) and (c) left ventriculogram showing apical filling defect suggestive of intraventricular tumour (AP and lateral views).*

inflow and outflow portions of the left ventricle. No thrombus was found in either ventricle. Histological examination showed zonal differentiation with a superficial layer and a granulation tissue layer containing dilated vascular channels and sparse chronic inflammatory infiltrate with no significant eosinophilic infiltration.

Endomyocardial biopsy of the right ventricle in cases 6 and 11 showed endocardial thickening with collagen and irregular elastic fibrils with no tissue eosinophilic infiltration.

Discussion

The main haemodynamic defect in these patients was restriction of ventricular filling and stroke output. Systolic contractile ability was not apparently affected in any of our patients though conceivably this could become impaired in the seriously involved ventricles. The presentation and clinical features varied considerably depending on the chambers involved and the severity of the haemodynamic disturbance.

SEVERE FORM WITH BIVENTRICULAR DYSFUNCTION

A severe form of the disorder with evidence of biventricular involvement and clinical resemblance to constrictive pericarditis was seen in 5 patients (cases 1 to 5). Three of these patients were subjected to exploratory thoracotomy because of residual doubt even after investigation, and in order to carry out a surgical biopsy. With our accumulated experience of the haemodynamic and angiocardiographic features together with a growing reliance on endomyocardial biopsy, which is very useful in this

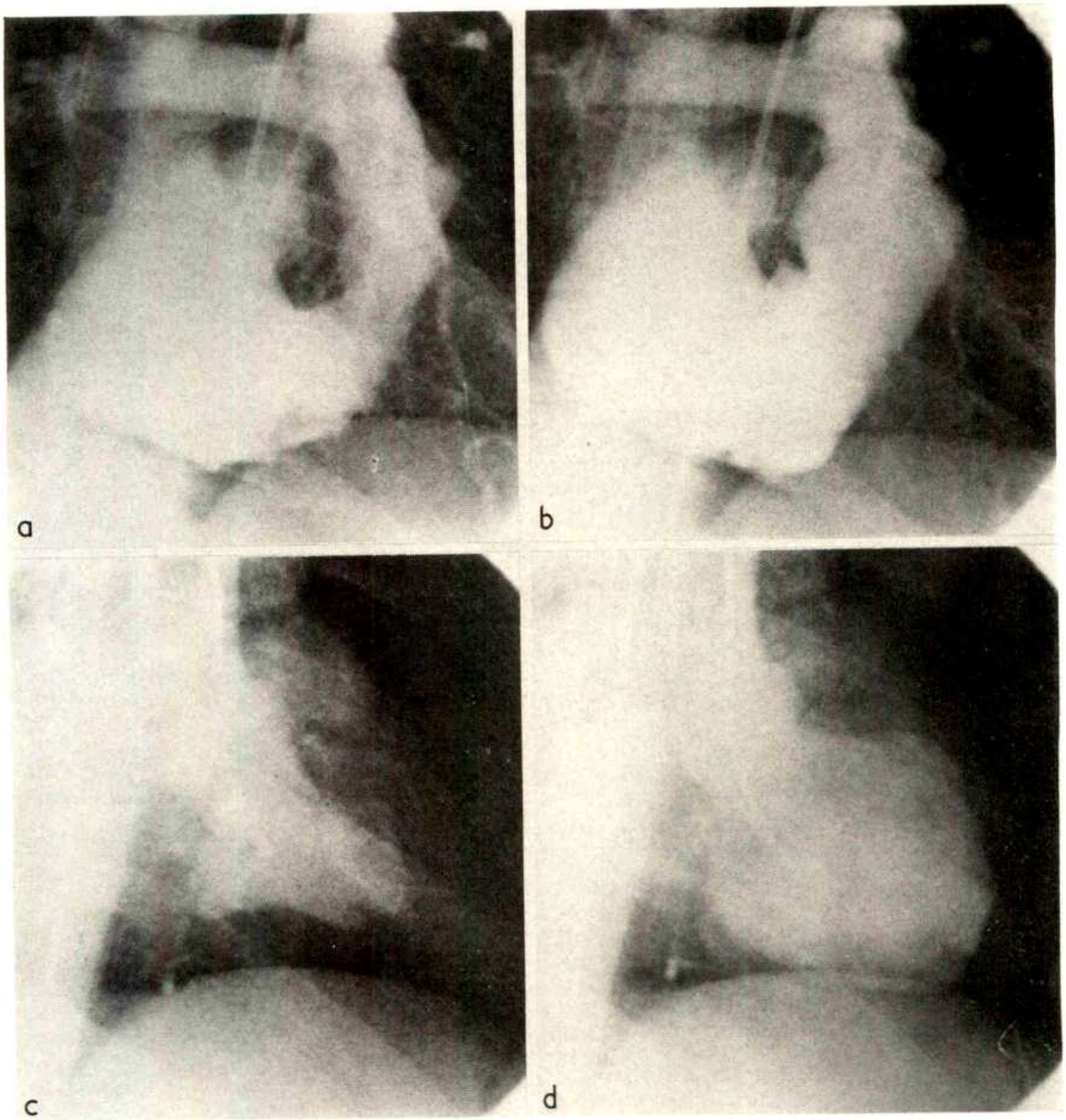

Fig. 8 *Case 6. (a) and (b) Right ventriculograms at end-systole and end-diastole, showing obliteration of the apex and preservation of infundibular contraction; (c) and (d) Left ventriculogram at end-systole and end-diastole. The ventricle is deformed with good contraction.*

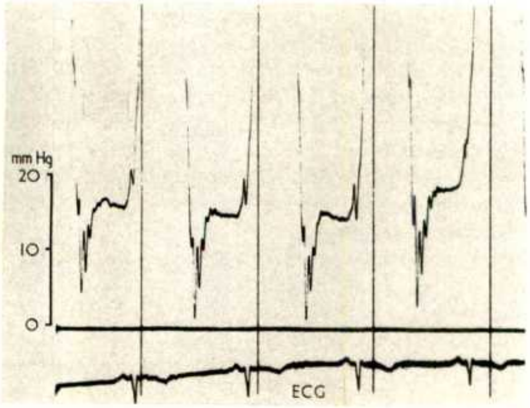

Fig. 9 *Case 8. Left ventricular diastolic pressure record with a 'dip and plateau' pattern.*

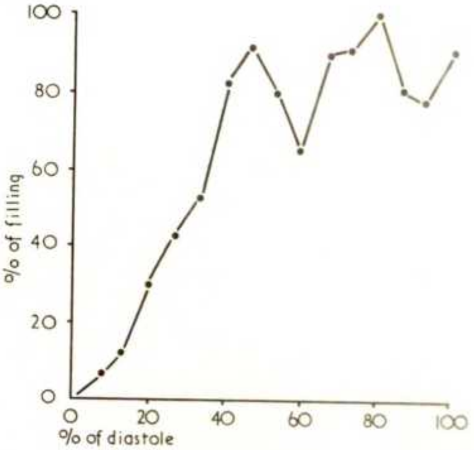

Fig. 11 *Case 2. Left ventricular filling plotted frame by frame from cineangiogram. There is rapid filling with 90 per cent of filling completed halfway through diastole. Fluctuations during the second half of diastole may be the result of lapping of blood through the mitral valve.*

disorder, the correct clinical diagnosis should now be made in all patients.

The characteristic loud and early third heart sounds reflected the characteristic pattern of ventricular filling which is illustrated in Fig. 11. Ventricular filling was completed early with little or no further filling in late diastole. This mirrored the apex cardiographic and echocardiographic feature of rapid outward movement of the posterior left ventricular wall with abrupt cessation. The timing of the third heart sounds was well within the range recorded in constrictive pericarditis (Wood, 1961). In cases 2 and 3, asynchronous left and right-sided third heart sounds were recorded and indicated unequal involvement of the two ventricles, a feature which should generally exclude constrictive pericarditis with the exception of those rare cases of constriction in the left atrioventricular groove. While the hearing of an apical mid-diastolic murmur might be the result of a localised pericardial constriction, the presence of systolic murmurs indicating atrioventricular valve regurgitation points to

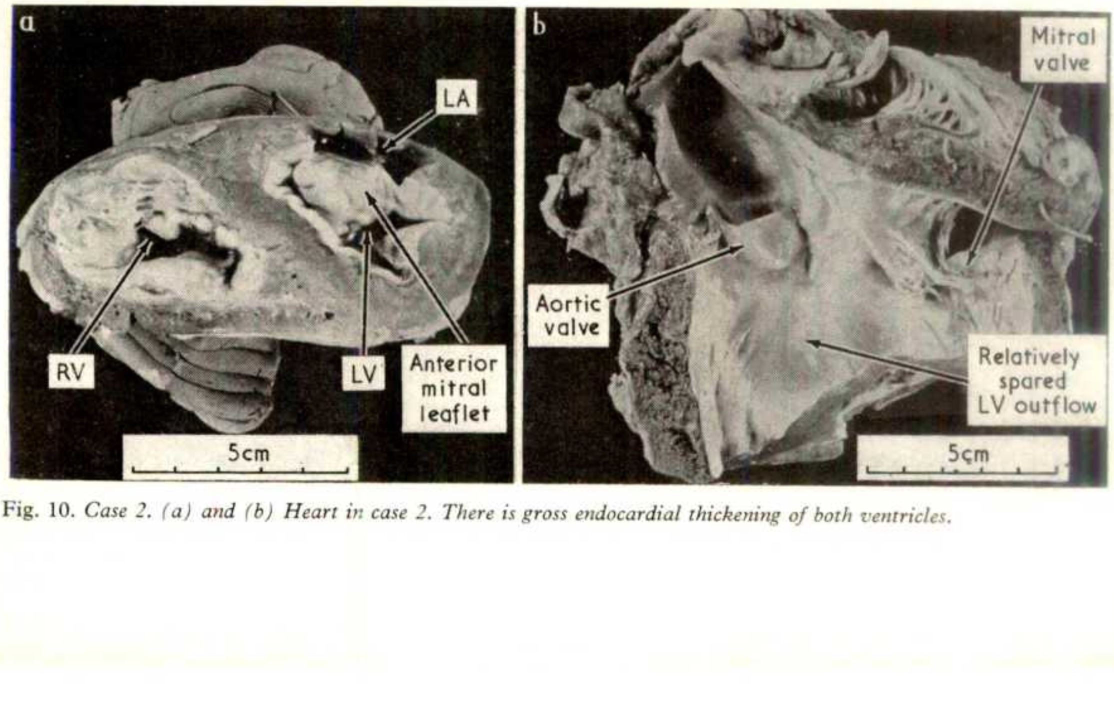

Fig. 10. *Case 2. (a) and (b) Heart in case 2. There is gross endocardial thickening of both ventricles.*

endocardial disease. In cases 1, 3, and 4, the left ventricular filling pressure was raised sufficiently to lead to pulmonary arterial hypertension. A raised pressure in the pulmonary artery is uncommon in constrictive pericarditis because sufficient rise in the left atrial pressure rarely occurs even in cases of extreme severity. In constrictive pericarditis, external restriction of filling affects both ventricles to an equal degree in most instances so that the end-diastolic pressures in the two ventricles are similar (Shabetai *et al.,* 1970). Both in pericardial constriction and in restrictive cardiomyopathy the dip and plateau form of the diastolic portion of the ventricular pressure record is seen, and in both conditions the early diastolic pressures are normal, in contrast to the raised early diastolic pressures which are seen in both hypertrophic cardiomyopathy (HOCM) and in amyloid heart disease.

The patients differed from those with amyloid heart disease, a condition which is often cited as an example of restrictive heart muscle disorder. In cardiac amyloidosis, as in restrictive cardiomyopathy, the left ventricular volume is normal at end-diastole but there is usually also distinct impairment of systolic emptying, a combination that results in the extremely low stroke volume, low pulse pressure, and low blood pressure, characteristic of amyloid heart disease. In amyloid heart disease the diastolic pressure in the left ventricle is high at the beginning of filling so that a true dip and plateau pressure pulse is rarely seen. We have previously shown that the left ventricle fills slowly throughout most of diastole in amyloid heart disease, and that this slow filling is reflected clinically by the absence of a third heart sound (Chew *et al.,* 1975).

The clinical and haemodynamic features of case 5 were those of predominant right ventricular involvement, and a right ventriculogram showed features of right-sided endomyocardial fibrosis (Cockshott *et al.,* 1967). The right ventricle was small, with obliteration of the apex, preservation of infundibular function, and tricuspid regurgitation. The reduced forward stroke output of the right ventricle in this type of case may completely mask the symptoms and signs of left ventricular dysfunction which was only revealed at catheterisation and ventriculography. The left ventriculogram showed an unusual filling defect at the apex suggestive of an intraventricular tumour (Fig. 7b). There was moderate mitral regurgitation into a normal sized left atrium. At exploratory cardiotomy, a mass, 3 cm in diameter, was found in the lower part of the left ventricular septum at a depth of about 2 mm below the endocardium. When excised, the mass was found to be composed of pale fibrous tissue with a necrotic centre, but there was no plane of cleavage to suggest a tumour. This case superficially resembled that described by Van der Hauwaert *et al.* (1965). These authors described a 16-month-old boy with eosinophilia and ventriculographic features akin to right-sided endomyocardial fibrosis; he was found at necropsy to have a large fibrotic mass in the right ventricle producing tricuspid stenosis.

Cases 6 and 7 had a striking eosinophilia and the clinical features of Löffler's eosinophilic endocarditis (Löffler, 1936; Brink and Weber, 1963; Scott and Bruce, 1975), though there were no embolic manifestations or electrocardiographic evidence of conduction defects. Our observations and those of Bell *at al.* (1976) show that the haemodynamic and ventriculographic findings in Löffler's endocarditis can be similar to those in severe endomyocardial fibrosis. As is characteristic of severe right-sided endomyocardial fibrosis, identical pressures were recorded in the right atrium and right ventricle in case 6 (Fig. 12). Ventriculographically both cases (6 and 7) had apical filling defects in the right ventricle, and a left ventriculogram in case 6 showed an undilated, well-contracting ventricle with an apical filling defect (Fig. 8).

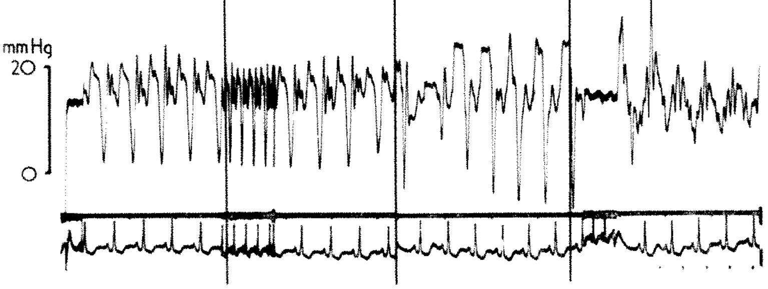

Fig. 12 *Case 6. Löffler's eosinophilic endocarditis. Identical pressure tracings from right ventricle, and from right and left atria, with prominent* y *descent in all.*

Exploratory thoracotomy and surgical biopsy was carried out in cases 2, 3, and 4. In each of these patients, the pericardium was found to be normal and the left ventricle small and thick walled. Histological examination of the myocardium showed a non-specific increase in interstitial fibrous tissue and some myocardial fibre hypertrophy. This well illustrates the difficulty in diagnosing a predominantly endocardial disease from a surgical biopsy as endocardium may not even be obtained.

The macroscopical and histological appearances in case 2 were typical of tropical biventricular endomyocardial fibrosis. The endocardium was grossly thickened and classically involved the apex and body of the right ventricular cavity and the inflow portion and the apex of the left ventricle. The endocardial thickening ceased abruptly at the junction of the inflow and outflow portions of the left ventricle with a rolled edge, as is commonly seen in endomyocardial fibrosis (Davies, 1968).

Transvenous right ventricular endomyocardial biopsy in case 6 with Löffler's eosinophilic endocarditis showed endocardial thickening with collagen and irregular elastic fibrils but no tissue eosinophilic infiltration.

LEFT VENTRICULAR DYSFUNCTION ONLY

Four of our cases (cases 8, 9, 10, and 11) had evidence of left ventricular disorder only. Three had atypical chest pain and were specifically referred for coronary arteriography. One was asymptomatic but had an abnormal electrocardiogram. These patients should be recognisable clinically by the unexpected third heart sound and the non-specific repolarisation changes on the electrocardiograms. The consistently raised filling pressure in the left ventricle and the shape of the left ventricular pressure pulse were characteristic.

The nature of the diastolic abnormality was studied in detail in cases 9, 10, and 11, in whom instantaneous left ventricular pressures and volumes were measured at 50 ms intervals throughout diastole (Fig. 13). At the moment of mitral valve opening the ventricular pressure and volume were both normal and filling was rapid, but in mid-diastole the pressure climbed steeply to an abnormally high level and after this time there was little further increase in ventricular volume. When examined against time, left ventricular filling was rapid and abruptly curtailed, as in case 2. Because contractile function was normal and the atrioventricular valves not involved in the endocardial process, this rapid ventricular filling enables these patients to compensate by tachycardia for reduced stroke output. The characteristic early and loud third heart sound is the clinical counterpart of this haemodynamic abnormality.

A contrast may be made with hypertrophic cardiomyopathy (HOCM) in which chest pain is also a common presenting symptom. In HOCM, the early diastolic pressures are abnormally high (Fig. 14) and rise further during diastole, culminating in an augmented *a* wave. Left ventriculography further differentiated between the two conditions. Unlike that in patients with HOCM, the left ventricle was normally shaped but showed normal or

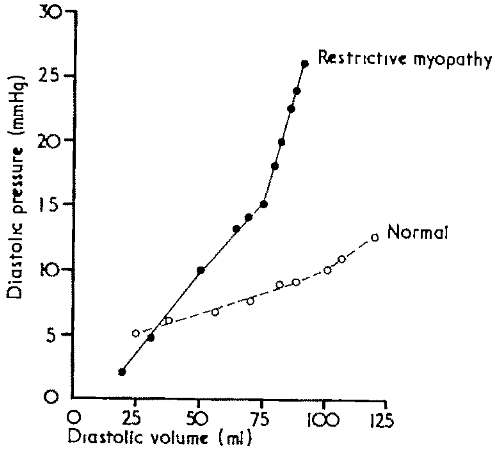

Fig. 13 *Case 11. Pressure-volume relation during one diastolic cycle.*

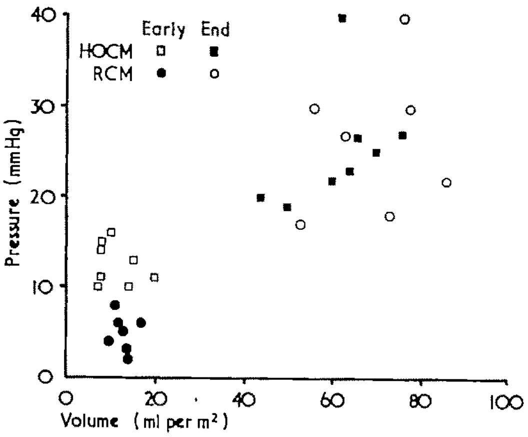

Fig. 14 *Left ventricular pressures and volumes at early and end-diastole in hypertrophic cardiomyopathy (HOCM) and restrictive cardiomyopathy (RCM).*

diminished trabeculation and reduced papillary muscle indentation. This gave the ventricle a smooth featureless appearance which was most obvious in severely affected cases though recognisable also in the milder ones.

USE OF ENDOMYOCARDIAL BIOPSY

A right ventricular biopsy in case 11 showed an excess of fibrous tissue which suggested that the disease process involved both ventricles even though the haemodynamic abnormality was confined to the left ventricle. In the absence of ventricular dilatation the finding of excessive fibrous tissue is highly suggestive of endomyocardial fibrosis. Left ventricular biopsy may be hazardous in patients with eosinophilia in whom mural thrombus may be present, and in any patient with features of restrictive cardiomyopathy, left ventriculography should probably always be carried out before attempting a biopsy from the left ventricle in order that intracavitary thrombus can be recognised. It is possible that right ventricular biopsy may be diagnostic even in patients without clinical right ventricular involvement, and that (as in case 11) left ventricular biopsy can be avoided.

POSSIBLE AETIOLOGY

A wealth of published material now exists on the occurrence of endomyocardial scarring and varying degrees of myocardial fibrosis outside tropical Africa. Cases have been reported from the USA (McKusick and Cochran, 1952; Thomas *et al.*, 1954; Clark *et al.*, 1956; McNamara *et al.*, 1959; Bishop *et al.*, 1968). Brazil (Andrade and Guimaraes, 1964), Ceylon (Nagaratnam and Dissanayake, 1959), South India (Samuel and Anklesaria, 1960), Japan (Nakajima *et al.*, 1961; Yoshida *et al.*, 1964), Jamaica (Stuart and Hayes, 1963), Malaya (La Brooy, 1957), Mexico (Contreras *et al.*, 1971), and Portugal (Coelho and Pimentel, 1963). In Britain, a number of cases have been reported (Lynch and Watt, 1957; Faruque 1963; Davies *et al.*, 1965). Black and Fowler (1965) encountered 5 cases of endomyocardial fibrosis with normal coronary arteries in a district general hospital and suggested that the condition might be more common than previously suspected.

The relation between these non-African cases of endomyocardial fibrosis and those of Ugandan type endomyocardial fibrosis as seen in tropical Africa and South America is difficult to ascertain. Connor *et al.* (1967, 1968) reviewed the findings in cases reported from Britain and the United States who were thought to have endomyocardial fibrosis but who had lived outside the tropics and found 4 that had extensive enough endocardial scarring and fibrosis to resemble Ugandan type endomyocardial fibrosis; these 4 cases were identical pathologically to our case 2 who came to necropsy.

Haemodynamically, our cases with biventricular disease are similar to those described as endomyocardial fibrosis from Africa and South America (Shillingford and Somers, 1961; Somers *et al.*, 1968; Guimarães *et al.*, 1974; Bertrand *et al.*, 1975). We have, however, shown that a mild form of the disorder exists in our society to which little attention has previously been paid. These cases in our series would have escaped recognition if they had not complained of chest pain. In medically less sophisticated societies, these mild and asymptomatic cases would probably not seek medical attention; this may explain the absence of descriptions of early or mild cases from those centres in tropical Africa from which the classical and clinically florid forms were originally described by Davies and his associates (Davies, 1948; Ball *et al.*, 1954).

None of the predisposing factors postulated in the pathogenesis of tropical endomyocardial fibrosis, such as filariasis (Ive *et al.*, 1967) or a diet rich in serotonin (Arnott, 1959) was relevant in our cases. None received drugs such as methysergide, busulphan, or daunorubicin which have recently been implicated in the development of endocardial fibrosis (Bana *et al.*, 1974; Weinberger *et al.*, 1975; Wilcox *et al.*, 1976).

Roberts *et al.* (1969, 1970) suggested that there might be a spectrum of eosinophilic heart disease ranging in severity from Löffler's eosinophilic endocarditis, the most acute and fatal form, to Ugandan type endomyocardial fibrosis. The evidence so far linking Löffler's eosinophilic endocarditis or the cardiac disorder occurring in other hypereosinophilic states with endomyocardial fibrosis without eosinophilia is reviewed by Oakley and Olsen (1977). Pathologically the two conditions are often indistinguishable (Brockington and Olsen, 1973; Olsen, 1975) and there have been reports of patients who present with an initial hypereosinophilic illness, survive, and who are found at necropsy to have endomyocardial fibrosis, in some with features identical to Ugandan type endomyocardial fibrosis (Blair *et al.*, 1974; Frenkel *et al.*, 1975; Libanoff and McMahon, 1976). Chusid *et al.* (1975) studied 14 patients presenting with the hypereosinophilic syndrome and in reviewing the published reports found clinical and pathological involvement of the heart in 95 per cent of the cases. Of those that came to necropsy, 41 per cent had thrombi closely adherent to endocardium, which was fibrotic in 31 per cent. The left ventricles appeared to be more severely affected than the right and both thrombus formation and endocardial fibrosis were more frequent at the apices than in the outflow tracts. Abnormal echocardiographic features consisting of left ventricular free wall and septal thickening were found in the majority of both asymptomatic and symptomatic cases.

Eosinophils are often abundant in areas of chronic inflammation though sparse at sites of acute inflammation. Several substances have chemotactic activity for eosinophils, including histamine and some antigen-antibody complexes (Archer, 1965) and some components of human complement (Lachmann *et al.*, 1970). Eosinophils can phagocytose immune complexes (Sabesin, 1963; Litt, 1964); morphological changes in the eosinophils are recognised and Connell (1968) pointed out that phagocytosis of immune complexes may produce vacuolation and degranulation. Some of Chusid's patients with a hypereosinophilic syndrome and a restrictive cardiac disorder showed such changes, and recently Spry and Tai (1976) showed that a proportion of the circulating eosinophils in such patients possessed receptors for rabbit IgG coated erythrocytes and actively phagocytosed lymphocytes coated with rabbit IgG or human C_3B. These abnormal eosinophils, therefore, had characteristics of mature or stimulated eosinophils with the capacity of responding to soluble substances in the blood by forming endocytic vacuoles leading to degranulation. This eosinophilic material which would normally not enter the blood stream where eosinophils are in tissue sites may itself be responsible for cardiac injury. Alternatively, it is possible that eosinophils migrating to the scene of immunological activity act in an entirely beneficial fashion through their phagocytic activity.

The absence of eosinophilia in some of our cases and in those from tropical Africa in no way invalidates this hypothesis. Eosinophilia may not be sustained even though the damage caused by or associated with it proceeds to healing with fibrosis, a stage of final scarring which we recognise as endomyocardial fibrosis when it occurs in the tropics and which we suggest occurs also in temperate climes and in milder form. Van der Geld and his associates in Uganda (1966) found a high incidence of circulating autoantibodies to heart muscle in endomyocardial fibrosis using immunological staining methods, and the incidence and severity of endocardial lesions in a population may reflect variable individual autoimmune responsiveness and account for the predilection of endomyocardial fibrosis in Uganda for immigrant groups from Rwanda and Burundi and relative immunity of the local indigenous Ganda tribe (Connor *et al.*, 1967, 1968). A less severe or less sustained endocardial process easily explains the existence of mild cases which are likely to have a good prognosis and would be unlikely to be recognised except for the chance recognition of a cardiac abnormality in an environment where diagnosis is aggressively pursued.

The group of patients described showed a restrictive cardiac disorder which varied in site and severity, thus accounting for the wide clinical spectrum. Our mildest cases, whose disease predominantly affected the left ventricle, presented because of chest pain which may be only a rare symptom in this disorder but which led in them to further investigation. Such patients should have a good prognosis, but in the more severe forms, with biventricular and valvular involvement, the prognosis may be much less good (D'Arbela *et al.*, 1972), though even these patients may live a number of years (Chusid *et al.*, 1975). It is in the most severely affected patients that endocardial resection and valve replacement may occasionally be carried out successfully and with benefit, as has recently been reported by a number of American and European workers (Lepley *et al.*, 1974; Dubost, 1975; Cachera *et al.*, 1976).

We thank Professor J. F. Goodwin for allowing us to include cases 3, 6, and 11; Drs. E. Besterman and R. Vecht for case 5; and Dr. E. G. J. Olsen for interpreting the biopsies, and for Fig. 10.

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Atresia of the right atrioventricular orifice

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The results are reported of a study of 83 necropsied hearts with atresia of the right atrioventricular orifice. It is emphasised that right atrial or atrioventricular orificial atresia is a better term to describe this anomaly than 'tricuspid atresia'. Use of the latter term can be confusing when the morphologically tricuspid valve is located beneath the left atrium. It is accepted that the definition employed may include cases in which the mitral valve may be atretic, blocking normal exit from the right atrium, but it is argued that such cases would present clinically as 'tricuspid atresia' and therefore are correctly designated as right atrial orificial atresia. The results show that the majority of hearts with right atrial orificial atresia have the ventricular morphology of primitive ventricle, most with, but a few without an outlet chamber. However, in a minority of hearts an imperforate membrane interposes between the right atrium and a formed but hypoplastic right ventricle. In two of the hearts, the imperforate membrane showed features of Ebstein's malformation. The hearts could be further subdivided according to the ventriculoarterial connection. Most had normally connected arteries (66 of 83), and all but 2 also had normal relations between the arteries; in these 2 hearts there was 'anatomically corrected malposition'. Twelve hearts showed transposition, one had double-outlet outlet chamber, and another persistent truncus arteriosus. The remaining 3 hearts, all without outlet chamber, had by definition a double outlet connection. A segmental approach provides the best way of classifying this anomaly, and an embryological explanation is offered for the variations in anatomy observed.

The classification of tricuspid atresia introduced by Edwards and Burchell (1949) has proved its value in clinical, surgical, and pathological settings. However, recent modifications of the original classification have perhaps detracted from its value. Using the modification suggested by Keith *et al.* (1958), atresia of either the right or left atrioventricular valves can correctly be described as tricuspid atresia. Definition of 'transposition' as applied to this classification varies considerably and is a potential source of further confusion. Thus, using the term 'transposition' to describe any anteriorly situated aorta, Tandon and Edwards (1974) described under the heading of 'tricuspid atresia with l-transposition' first, hearts with right atrioventricular valve atresia in which the aorta arose from the left ventricle and secondly, hearts with left atrioventricular valve atresia in which the aorta arose from the right ventricle.

With the advent of radical palliative surgery for tricuspid atresia (Fontan and Baudet, 1971), it is desirable to have a system of nomenclature which avoids these discrepancies. Any successful nomenclature should permit accurate description of hearts in all aspects of their anatomy, in particular with regard to the site of atrial orificial atresia and to the ventricular morphology and ventriculoarterial connections. The segmental approach promoted by Van Praagh and his colleagues (Van Praagh *et al.*, 1964; Melhuish and Van Praagh, 1968; Van Praagh, 1972) is ideally suited for this purpose. We have therefore analysed a series of specimens with right atrial orificial atresia using this approach.

Materials and methods

The 83 hearts studied were all those with atresia of the right atrioventricular orifice in the pathological collections of the Brompton Hospital, London; Royal Liverpool Children's Hospital; Grimsby General Hospital; Wilhelmina Gasthuis, Amsterdam; Sint Antonius Ziekehuis, Utrecht; and selected specimens from the Department of Anatomy, University of Leiden. In all instances the

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hearts were studied so as to elucidate their segmental arrangement, paying particular attention to the ventricular morphology, and the nature of associated anomalies. Twelve of the hearts were also studied by serial histological sectioning of the atrioventricular junctions primarily in order to ascertain the disposition of the conducting tissue (J. L. Wilkinson, A. Smith, A. E. Becker, and R. H. Anderson, unpublished observations). Certain of these histological findings are pertinent to the present investigation, and will be discussed where relevant.

Definitions and terms

(1) ATRIAL SITUS

Situs solitus is present when the morphologically right atrium is right sided and the left atrium is left sided (Shinebourne *et al.*, 1976). The other varieties of atrial situs are *situs inversus* and *situs ambiguus.*

(2) VENTRICULAR MORPHOLOGY

The terms *right ventricle* and *left ventricle* will only be used in this report when each ventricular chamber is in potential communication with a separate atrial chamber, and each ventricular chamber contains the complete tension apparatus of the connecting atrioventricular valve (Fig. 1).

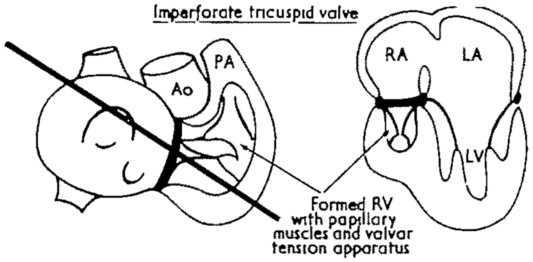

Imperforate tricuspid valve
PA
Ao
RA
LA
LV
Formed RV with papillary muscles and valvar tension apparatus

Fig. 1 *Diagram illustrating the concept of a heart with formed right and left ventricles, but an imperforate membrane between the right atrium and the right ventricle. The latter chamber contains valvar tension apparatus.*

In the situation in which a single atrioventricular valve is present between the left atrium and a ventricular chamber, and the blind-ending right atrium *is also in potential communication with the chamber receiving the single antrioventricular valve,* then the ventricular morphology is considered to be a variant of *primitive (single* or *common) ventricle* (Macartney *et al.*, 1976; Shinebourne *et al.*, 1976). In this situation the chamber receiving the single atrioventricular valve is termed the *main chamber.* If a smaller anterior chamber is also present it is termed the *outlet chamber* (Fig. 2). The foramen

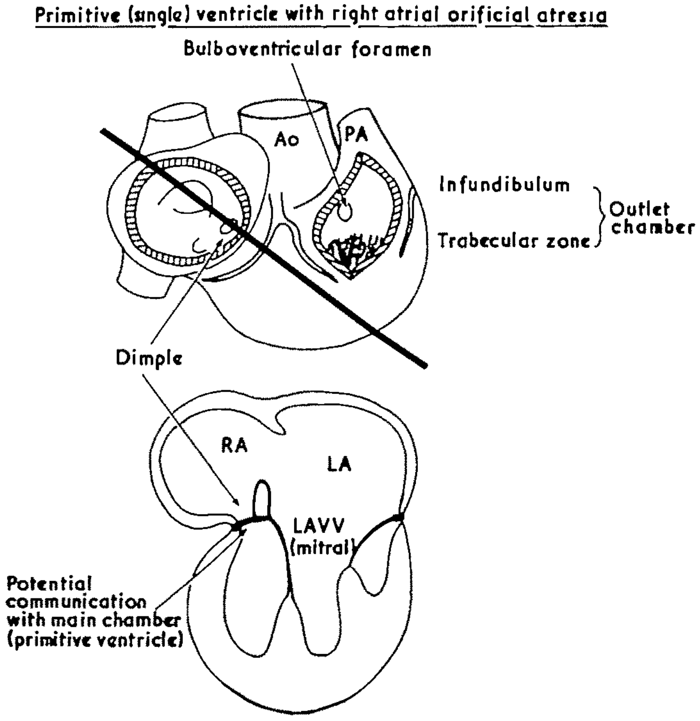
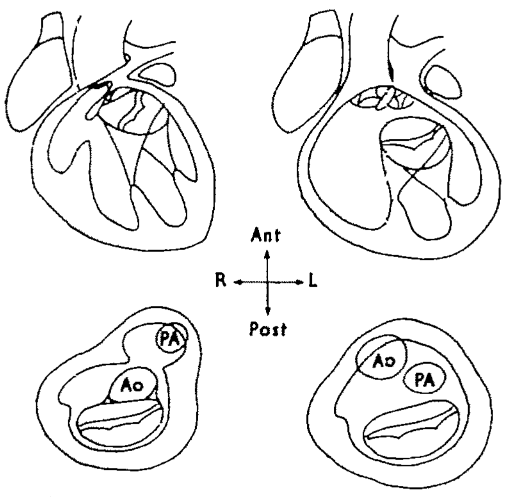

Primitive (single) ventricle with right atrial orificial atresia
Bulboventricular foramen
Ao
PA
Infundibulum
Trabecular zone
Outlet chamber
Dimple
RA
LA
LAVV (mitral)
Potential communication with main chamber (primitive ventricle)

Fig. 2 *Diagram illustrating the concept of a univentricular heart with right atrial orificial atresia. The blind ending right atrium is in potential communication* only *with the main chamber which receives the left atrioventricular valve. The anterior chamber is an outlet chamber,* not *a true right ventricle, exhibiting only infundibular and trabeculated zones. It does* not *contain valvar tension apparatus. The heart is, therefore, a variant of primitive ventricle with outlet chamber, and the communication between the chambers is the secondary bulboventricular foramen.*

between the main and outlet chambers is described as the *bulboventricular foramen*, remembering that if one great artery arises from the main chamber the foramen should strictly be termed the *secondary* bulboventricular foramen. (Compare closure of the interventricular defect by Van Mierop *et al.* (1963).) When a single ventricular chamber receives a single atrioventricular valve, supports both great arteries, and also is in potential communication with the blind-ending right atrium, there being no evidence of an anterior outlet chamber, then the anomaly is described as *primitive (single* or *common) ventricle without outlet chamber* (Fig. 3). The single atrioventricular valve present in the hearts to be described is termed the *left atrioventricular valve.* Its morphology will be described where pertinent. Since the blind-ending right atrium does not always have a fibrous membrane interposing between it and a ventricular chamber, the situation will be described as *right atrial orificial atresia* rather than as valve atresia. If a membrane is present, then its morphology will be described.

Primitive ventricle with right atrial orificial atresia



a) With outlet chamber 74 cases

b) Without outlet chamber 3 cases

Fig. 3 *Diagram illustrating the concept of right atrial orificial atresia in hearts with (a) primitive ventricle with outlet chamber and (b) primitive ventricle* without *outlet chamber. The numbers indicate the total of cases studied in each category. The upper panels are frontal sections, the lower horizontal sections through the heart just beneath the atrioventricular junction.*

(3) VENTRICULOARTERIAL CONNECTIONS (Fig. 4)

Normal connections describe the situation in which the aorta arises from the left ventricle or from the main chamber, and the pulmonary artery from the right ventricle or from the outlet chamber. Usually with normal connections the aortic valve is posterior and to the right of the pulmonary valve. This is described as *normal relations* (Fig. 4A). Occasionally normal connections exist with the aortic valve in anterior, left-sided position (Fig. 4B). This is described as *normal connections with l-malposition* or 'anatomically corrected malposition'. *Transposition* is present only when the aorta arises from the right ventricle (or from an outlet chamber) and the pulmonary artery from the left ventricle (or from the main chamber). The prefixes *d-* and *l-* refer to the position of the aortic valve relative to the pulmonary valve whether describing malposition or transposition (Fig. 4C and D). When more than 1½ great arteries arise from the same chamber, the connection is described as *double-outlet main chamber* or *double-outlet outlet chamber* (Fig. 4E); the great arteries in double-outlet chambers are described in terms of d- or l-malposition. When a single arterial trunk leaves the base of the heart and when this single artery gives rise to the aorta, one or both pulmonary arteries, and the coronary arteries, it is described as a persistent truncus arteriosus (Fig. 4F). Other variants of single trunk are single aortic trunk with pulmonary atresia and single pulmonary trunk with aortic atresia.

(4) VENTRICULAR MUSCLE BUNDLES

In the hearts studied the muscular septum interposing between the aortic and pulmonary valves is described as the *infundibular septum*. Previously this structure has been termed the conus septum (Anderson *et al.*, 1974b). If a muscular fold separates the posterior semilunar valve from the atrioventricular valve it is termed the *ventriculo-infundibular fold*. This previously has been termed the conoventricular flange (Anderson *et al.*, 1974b).

Results

A. ATRIAL ANATOMY

All the hearts studied had situs solitus. The right atrium, therefore, received the systemic venous return. The only exit from the right atrial chamber was through an interatrial communication. In 77 hearts, the communication was either a secundum atrial septal defect or a widely patent foramen ovale. In 6 hearts the defect was of the ostium primum variety, in each case with a cleft in the left atrioventricular valve (Fig. 5). A further significant

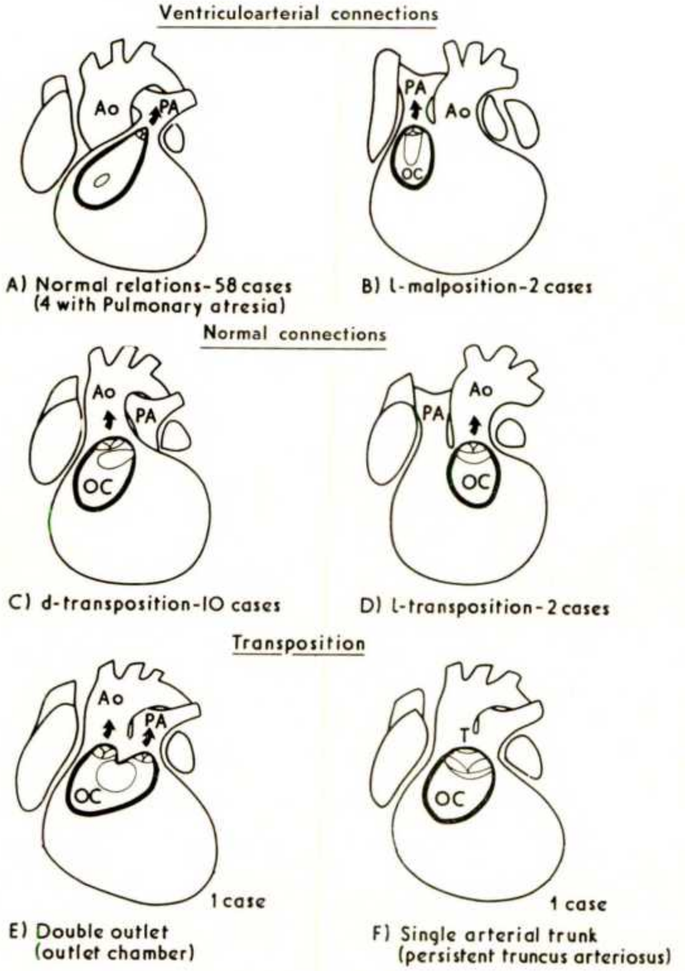

Ventriculoarterial connections
Ao
PA
A) Normal relations-58 cases (4 with Pulmonary atresia)
PA
Ao
OC
B) l-malposition-2 cases
Normal connections
Ao
PA
OC
C) d-transposition-10 cases
Ao
PA
OC
D) l-transposition-2 cases
Transposition
Ao
PA
OC
1 case
E) Double outlet (outlet chamber)
T
OC
1 case
F) Single arterial trunk (persistent truncus arteriosus)

Fig. 4 *Diagram illustrating ventriculoarterial connections in 74 cases of primitive ventricle with outlet chamber and right atrial orificial atresia, and the number of specimens studied in each category.*

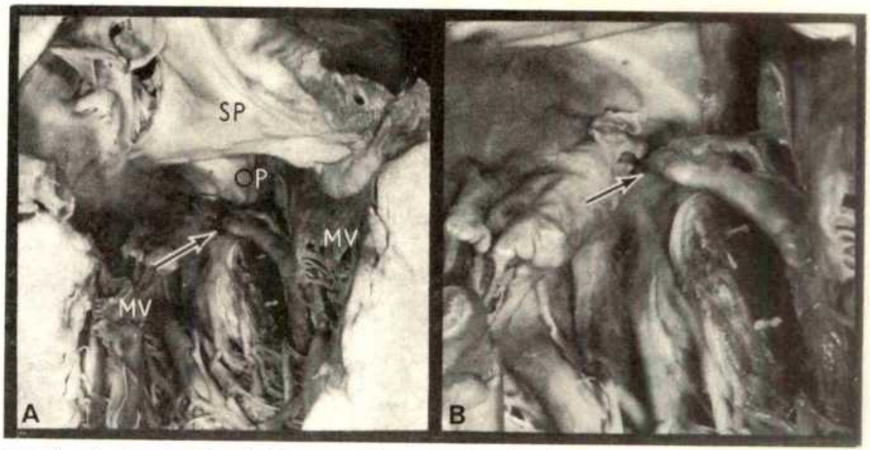


Fig. 5 *Photographs of a heart with primitive ventricle and outlet chamber and right atrial orificial atresia, an ostium primum defect, and a cleft mitral valve. (A) View from posterior aspect of main chamber. The free lower edge of the septum primum (SP) is seen, with an ostium primum (OP) defect beneath it. The mitral valve (MV) has a cleft (arrowed) in its anterior leaflet, and the valve orifice extends into the right atrium. The cut seen is through the right lateral wall of the heart. (B) Magnified view of cleft in anterior mitral leaflet.*

feature of right atrial anatomy in approximately a third of the hearts studied was persistence of portions of the embryonic venous valves. In 2 instances the valves were almost complete and partitioned the auricular part of the chamber from the sinus venarum (Gerlis and Anderson, 1976). In one heart, Fontan repair had been attempted, and the Eustachian valve formed a veil across the prosthetic inferior vena caval valve which had been inserted, separating it from the atrial insertion of the conduit. Discrete 'dimples' in the floor of the right atrium were observed in 36 of the hearts studied. The left atrium in all hearts received the pulmonary venous return and, via the interatrial communication, the systemic venous return.

B. VENTRICULAR MORPHOLOGY

In 6 hearts formed right and left ventricles were identified (Fig. 1). An imperforate membrane was present in the floor of the right atrium separating it from the formed right ventricle. On its ventricular aspect the membrane was attached to hypoplastic valvar tension apparatus. In 4 of the 6, the right ventricle was small and hypoplastic and the infundibulum was also blind ending. These hearts were, therefore, examples of pulmonary atresia with intact septum. In one the cavity extended as multiple sinusoids into the septum, which bulged into the aortic outflow tract. In the other 2 hearts, the imperforate membrane between right atrium and right ventricle was displaced distally to the

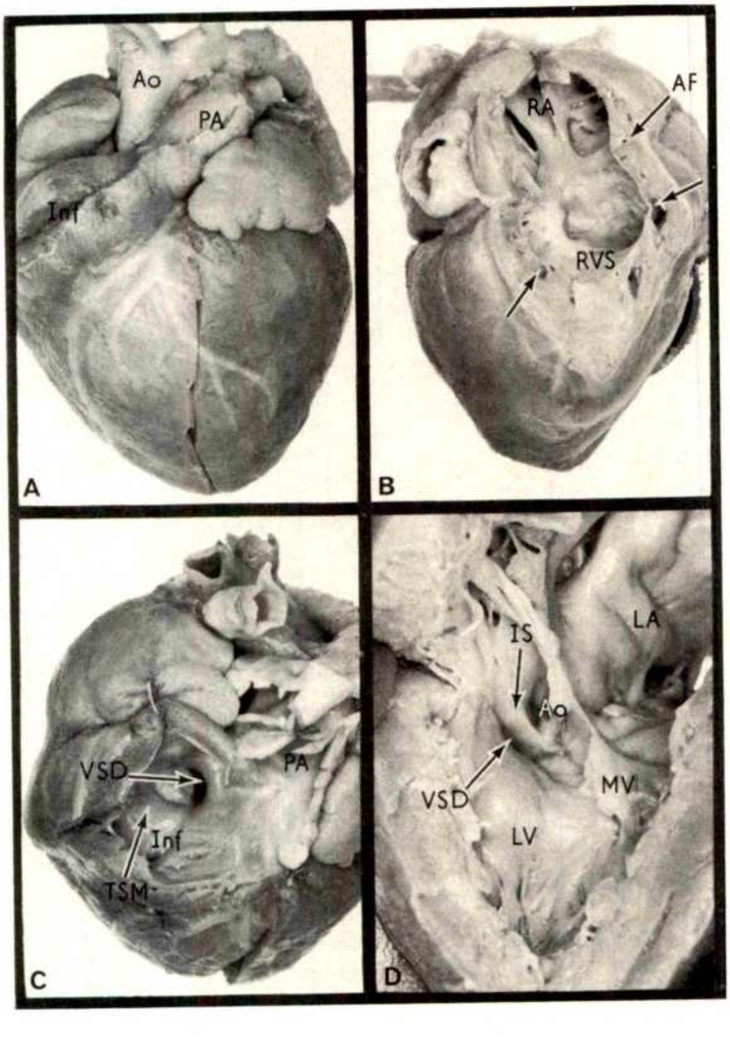


Fig. 6 *Photographs of a heart with formed right and left ventricles and an imperforate Ebstein's anomaly. (A) An anterior view of the heart. The arteries (Ao, PA) are normally connected and normally related. (B) The right side of the heart after removal of its right posterolateral wall. The right atrium (RA) leads to the right ventricular sinus (RVS) but egress of blood is blocked by an imperforate tricuspid valve. The ventricular origin of the valve (arrows) is well below the annulus fibrosus (AF), indicating an Ebstein anomaly. (C) The opened infundibulum (Inf). Blood reaches the pulmonary artery (PA) through a large ventricular septal defect (VSD), and the imperforate tricuspid valve is seen through the defect. Note also the prominent trabecula septomarginalis forming a partial septum between the infundibulum and sinus of the right ventricle. This structure could also be considered a remnant of the bulboventricular septum. (D) The left-sided chamber is a morphological left ventricle (LV). The defect from this chamber to the infundibulum is now bounded by the interventricular septum and the infundibular septum (IS) not by the right bulboventricular ridge as in the hearts with primitive ventricle (*vide infra*). LA, left atrium; MV, mitral valve; Ao, aorta.*

junction of ventricular inflow and outflow portions. They were, therefore, examples of imperforate Ebstein's anomaly. One of these has been described elsewhere (Gerlis and Anderson, 1976); the other (Fig. 6) had a large ventricular septal defect between the left ventricle and the right ventricular infundibulum, which supported a good sized pulmonary artery.

In 77 hearts the blind ending right atrium was not in potential communication with an anterior ventricle, but with the same ventricular chamber as received the left atrioventricular valve (Fig. 7 and 8). All these hearts were, therefore, examples of primitive (single or common) ventricle. In one heart (Fig. 7) a fibrous membrane at the site of the dimple formed a discrete aneurysm protruding from the floor of the right atrium into the main chamber. In 36 of the remaining hearts the right atrial 'dimple' overlaid the central fibrous body, and was again the potential communication with the main chamber. In 34 hearts, discrete 'dimples' were not observed, but dissection revealed that the right atrial floor was in potential communication only with the main chamber (Fig. 8). In a further 6 hearts, ostium primum defects existed through which the right atrium was in direct communica-

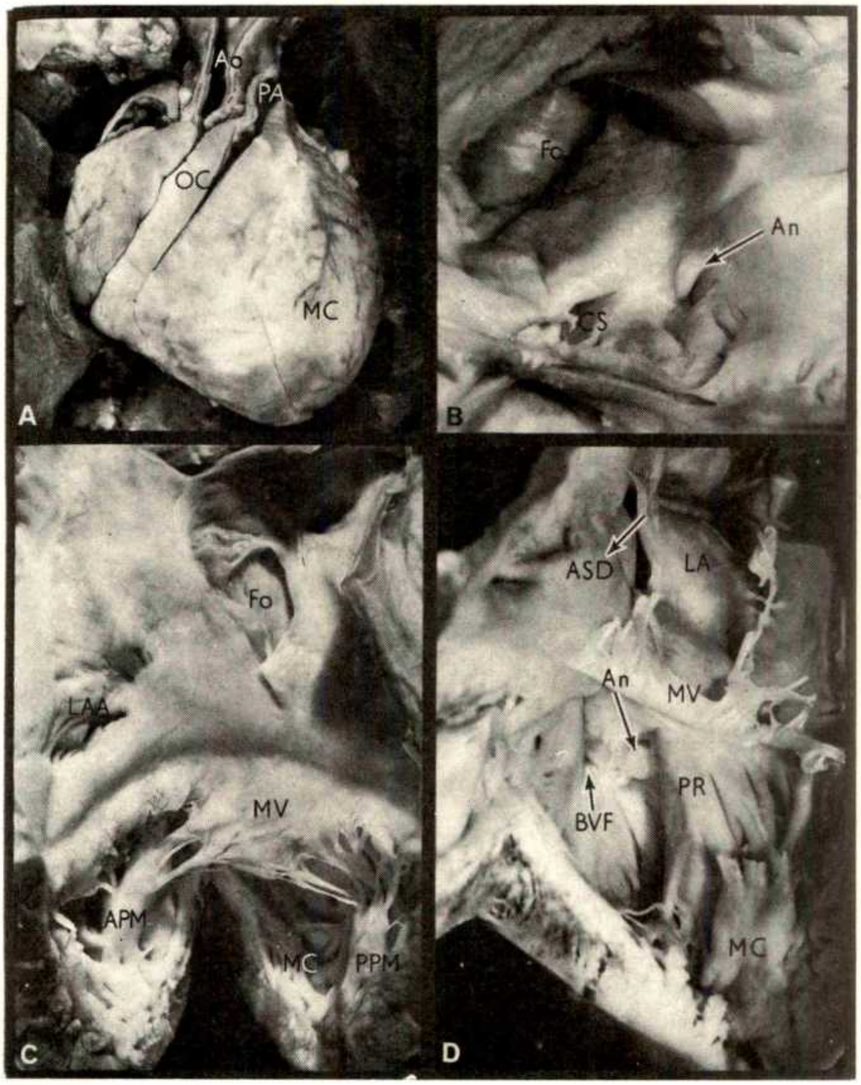


Fig. 7 *Photographs of a specimen of primitive ventricle with outlet chamber, right atrial orificial atresia, and with an aneurysmal 'dimple'. (A) Anterior view of the heart (OC, outlet chamber; MC, main chamber; Ao, aorta; PA, pulmonary artery). (B) Right atrial anatomy. The dimple is large and aneurysmal (An) (FO, foramen ovale; CS, coronary sinus). (C) Left atrium communicating with main chamber through a normal mitral valve (MV) (LAA, left auricular appendage; APM, PPM, anterior and posterior papillary muscles). (D) After retraction of the mitral valve, the aneurysm is seen pointing into the large cleft between the well formed posterior ridge (PR) and the bulboventricular septum. We believe this cleft to represent the unexpanded right ventricular inflow tract (BVF, bulvoventricular foramen).*

tion with the main chamber (Fig. 5). The histological studies in 12 hearts confirmed these atrioventricular relations, and showed that the atrioventricular incisura always interposed between the right atrial floor and the outlet chamber.

In 74 of the 77 hearts the ventricular morphology was that of primitive ventricle with outlet chamber. In the remaining 3 hearts there was only one ventricular chamber, which received the left atrioventricular valve and gave rise to both great arteries (Fig. 9). In primitive ventricle without outlet chamber the ventriculoarterial connection must by definition be one of double outlet (Shinebourne *et al.*, 1976). There was d-malposition in two of these hearts and l-malposition in the third. When an outlet chamber was present, it was anterior and to the right in 71 specimens and to the left in 3. The outlet chamber morphology varied according to the ventriculoarterial connection. With normal ventriculoarterial connection, the outlet chambers had long infundibular segments and smaller apically trabeculated portions (Fig. 2, 10). In contrast, when

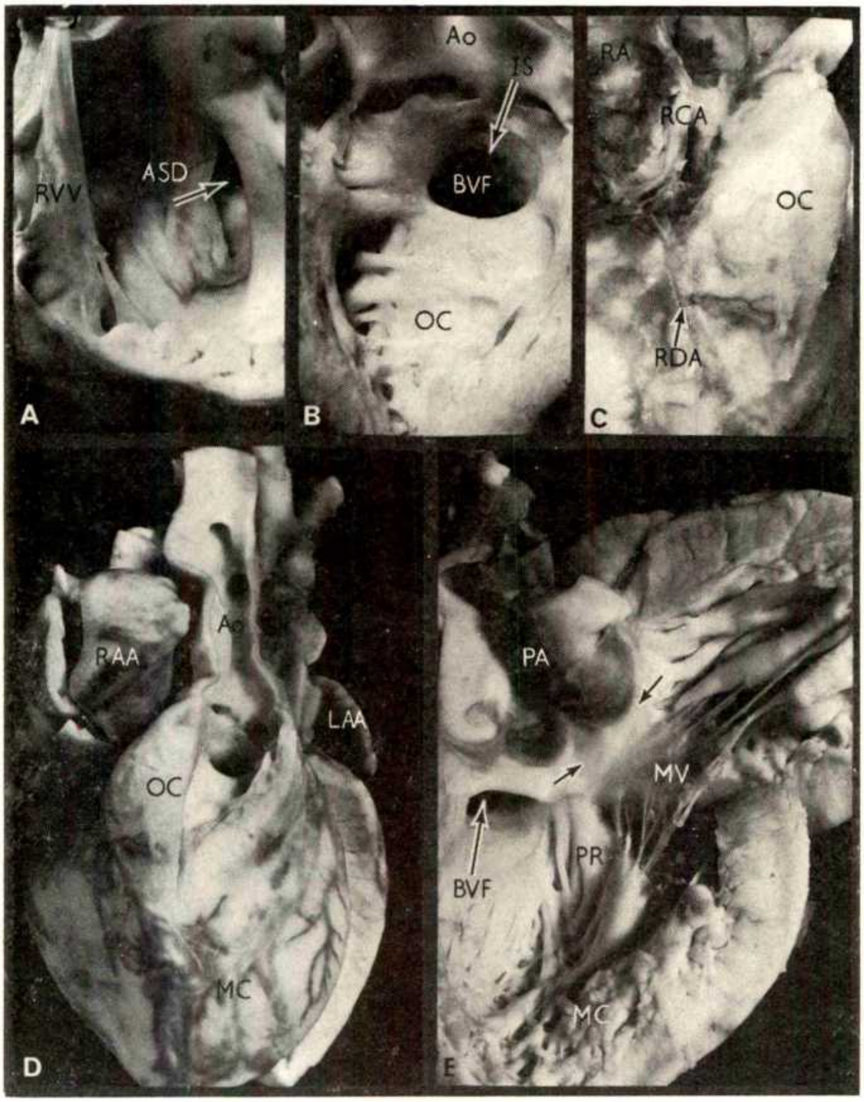


Fig. 8 *Photographs of a specimen of primitive ventricle with outlet chamber, right atrial orificial atresia, and transposed great arteries. The general view of the heart is seen in (D) (RAA-right auricular appendage). (A) Detail of the blind-ending right atrium. Note the prominent right venous valve (RVV). (B) Detail of the anterior aspect of the opened outlet chamber. Note that the infundibular septum is short so that the bulboventricular foramen opens directly beneath the aortic valve (compare Fig. 8B, 10B). (C) Detail of a right oblique view of the heart. The right coronary artery (RCA) runs between the right atrium and the outlet chamber, and its descending branch (RDA) delimits the outlet chamber. The chamber is not in contact with the right atrium. (E) Main chamber giving rise to the pulmonary artery. Note the prominent posterior ridge and mitral-pulmonary valvar continuity (between arrows). Other abbreviations as before.*

transposition was present the infundibular segment was much shorter and the trabeculated zone more prominent (Fig. 8).

The trabeculations of the main chamber resembled those of the normal left ventricle in all cases, but were frequently much coarser than normal (Fig. 10). There were several other differences between the main chamber and a normal left ventricle. The septal surface was much smaller, was orientated in the frontal plane, and was frequently trabeculated. The bulboventricular defect was separated from the area of the central fibrous body by direct fusion of the infundibular septum with the bulboventricular septum. The aortic valve in hearts with normally connected arteries was, therefore, separated from the defect by a muscular bar, unlike the situation seen in isolated ventricular septal defect with normally connected arteries (compare Fig. 11A and B). Another unusual feature of the main chamber was the presence of a prominent posterior trabeculation. In some hearts this ridge was sufficiently prominent to divide the chamber into large left and smaller right-sided portions (Fig. 10). In all but two hearts the valve entering the main chamber had the morphological characteristics of a mitral valve (Fig. 7, 8). In these two hearts, both with left-sided outlet chambers, there were morphologically tricuspid valves between the left atrium and the main chamber; in both hearts the outlet chamber was larger with a prominent trabeculated pouch and the bulboventricular septum was straddled by the left atrioventricular valve (see Fig. 13). In the other

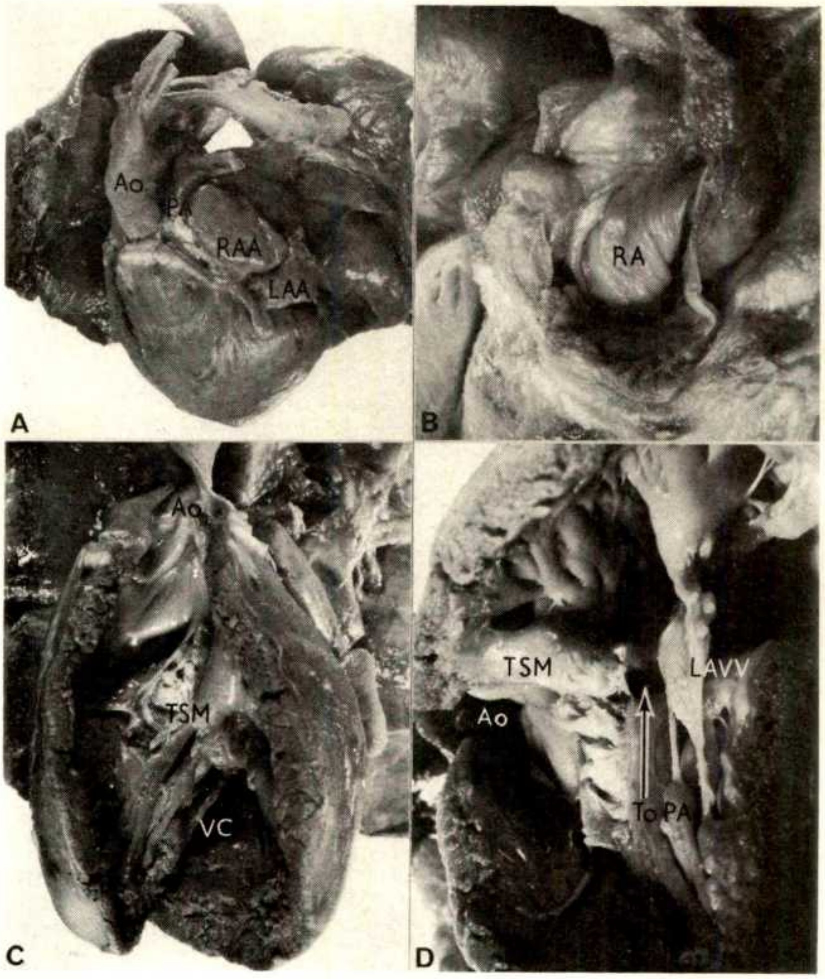


Fig. 9 *Photographs of a specimen of primitive ventricle,* without *outlet chamber, and right atrial orificial atresia. (A) The general view of the heart. The auricles (RAA, LAA) are juxtaposed to the left of the great arteries, the aorta (Ao) being anterior and to the right of the pulmonary artery (PA). (B) The blind-ending right atrium (RA). (C) The anterior aorta (Ao) arises from the sole ventricular chamber (VC). The cavity of the ventricle is spanned by a free running strand which represents the trabecula septomarginalis (TSM). These relations are better illustrated in (D), taken from the apex of the ventricle. The single chamber receives the left atrioventricular valve (LAVV) and gives rise to both great arteries (Ao, PA), which are separated by the infundibular septum. The ventriculoarterial connection is one of double outlet ventricle.*

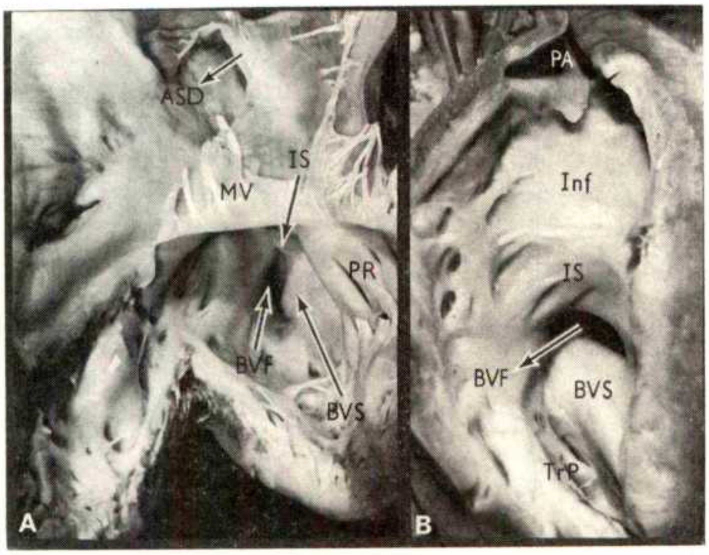


Fig. 10 *Further views of the case of primitive ventricle with outlet chamber, right atrial orificial atresia, and aneurysmal 'dimple' illustrated in Fig. 7. (A) The relation of the bulboventricular foramen to the posterior ridge. The inferior edge of the infundibular septum (IS) and the bulboventricular septum (BVS) separate the dimple from the outlet chamber. (B) The anterior aspect of the outlet chamber. It differs in morphology from that seen in Fig. 8, by virtue of the deep infundibulum (Inf) beneath the pulmonary valve. It possessed an extensive trabeculated apical pouch (TrP). However, it does not contain tension apparatus and does* not *receive the aneurysmal dimple (see Fig. 7).*

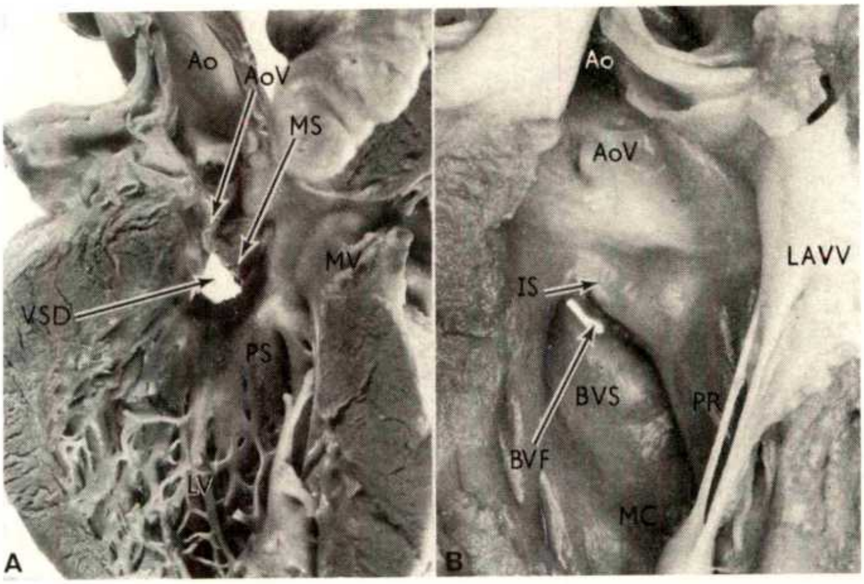


Fig. 11 *Photographs illustrating the differences between an isolated ventricular septal defect (VSD) in a heart with atrioventricular concordance (A), and a secondary bulboventricular foramen (BVF) in a heart with primitive ventricle with outlet chamber and right atrial orificial atresia (B). (A) Viewed from the left ventricle (LV); (B) from the main chamber (MC). Note that in the isolated defect, the roof is the aortic valve (AoV) and the partially formed interventricular segment of the membranous septum (MS). Because of the failure of formation of the right ventricular inflow tract in the specimen shown in (B), the interventricular segment of the membranous septum is lacking. The foramen is bounded instead by the infundibular septum (IS). Note also the difference in orientation between the posterior interventricular septum (PS) and the bulboventricular septum (BVS). Other abbreviations as above.*

specimen with right atrial orificial atresia and left-sided outlet chamber the left atrioventricular valve was morphologically a mitral valve (Fig. 12).

C. VENTRICULOARTERIAL CONNECTIONS

All the 6 hearts with atrioventricular concordance (right atrium separated from right ventricle by imperforate membrane) had normal ventriculoarterial connections, albeit with pulmonary atresia in 4 cases. Connections were very variable when the ventricular morphology was that of primitive ventricle (Fig. 4). Normal connections (60 of 77 hearts) were most frequently encountered, usually with normal relations (58 of 60). Four of these hearts had pulmonary atresia. Two of the hearts with normal connections had l-malpositioned aortae (anatomically corrected malposition). Twelve hearts had transposition, 10 with d-transposed aortae. It was noteworthy that 1 of 2 cases with l-transposition had a left-sided mitral valve. The 3 hearts without outlet chambers had double outlet chambers by definition, 2 with d- and 1 with l-malposition. One additional heart had a double-outlet connection, from the outlet chamber. One specimen had a persistent truncus arteriosus.

D. PULMONARY AND AORTIC STENOSIS

The most frequent source of stenosis was a constrictive bulboventricular foramen in hearts with primitive ventricle. Such a constriction produced

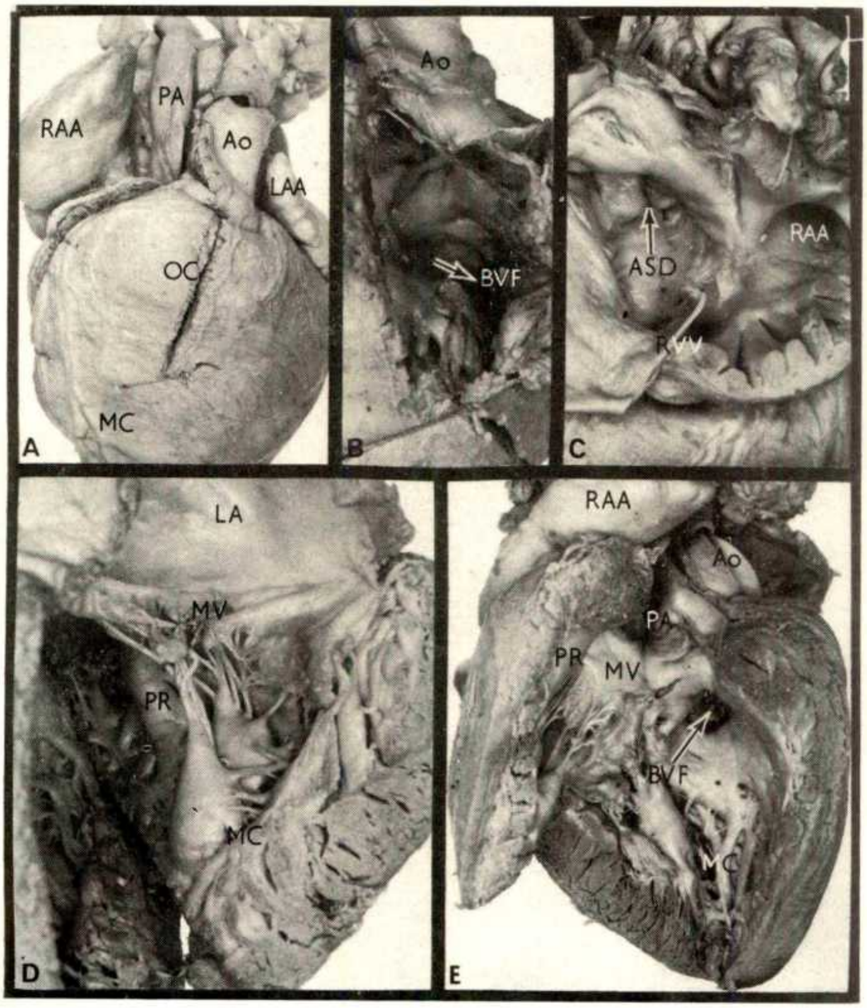


Fig. 12 *Photographs of a heart with primitive ventricle outlet chamber, right atrial orificial atresia, and l-transposition. (A) Anterior view of the heart. The outlet chamber is anterior to the main chamber and the aorta is left sided. The opened outlet chamber is seen in (B). It is small and the bulboventricular foramen opens directly beneath the aortic valve. (C) The blind-ending right atrium. Note the prominent venous valve (RVV). (D) Main chamber opened from behind and from the left. Note the typical mitral valve and the prominent posterior ridge (PR). (E) Viewed from the right through the cut visible in (D). The front of the mitral valve is seen with pulmonary-mitral valvar continuity. Despite the presence of right atrial orificial atresia and a left-sided mitral valve the aorta and bulboventricular foramen (BVF) are both* left *sided. Other abbreviations as above.*

pulmonary stenosis in 30 hearts with normally connected arteries, and aortic stenosis with associated isthmal hypoplasia in 5 hearts with transposition (Fig. 14). Another source of pulmonary stenosis in the presence of normal connections was a constriction between the trabeculated and infundibular segments of the outlet chamber; this was seen in 4 hearts in addition to stenosis at the bulboventricular foramen. Valvar stenosis also frequently accompanied bulboventricular stenosis but in 3 cases was the sole cause. In one further case, fibrous tissue from the underside of the infundibular septum obstructed the bulboventricular foramen. Pulmonary stenosis was not seen in association with transposition.

E. ADDITIONAL ANOMALIES

Juxtaposition of the auricles was encountered in 4 hearts. Three had 1-malpositioned aortae, 2 of these with normal ventriculoarterial connections (anatomically corrected malposition).

Discussion

Our investigation has shown, as others have found before (Okin *et al.*, 1969; Van Praagh *et al.*, 1971;

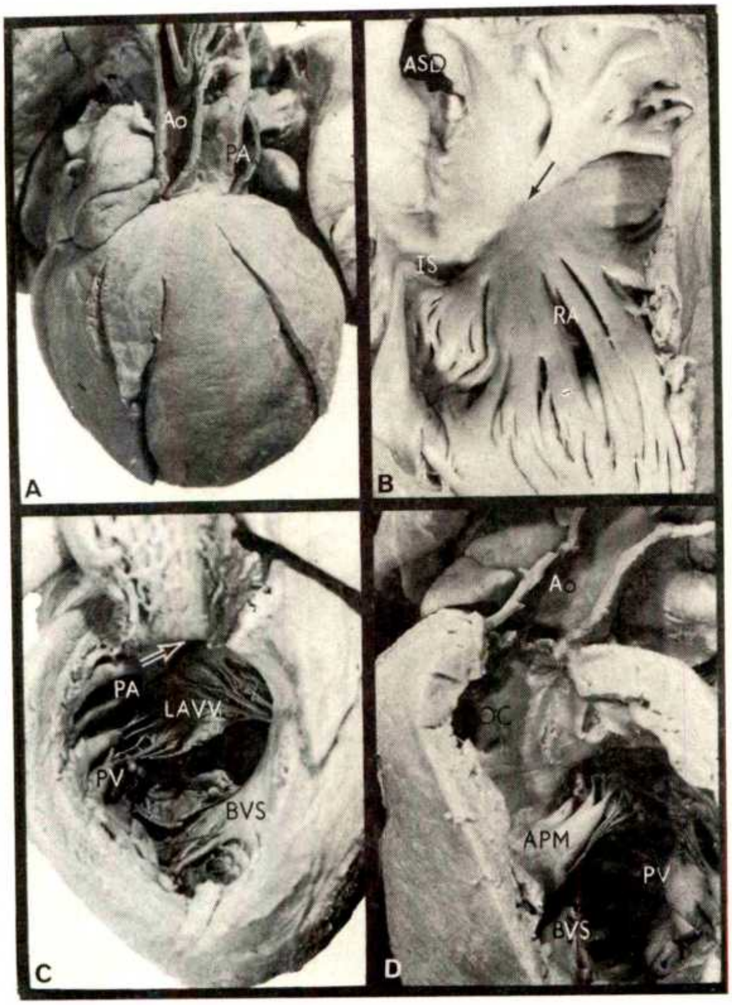


Fig. 13 *Photographs of a heart with primitive ventricle, outlet chamber, right atrial orificial atresia, straddling left atrioventricular valve, and d-transposition. (A) Anterior view of the heart. Note the right-sided aorta and the position of the two incisions into the ventricular mass. (B) The interior of the right atrium. It is blind ending with a small dimple (arrowed). The only route for systemic venous blood is through the atrial septal defect. (C) Ventricular morphology viewed through the right-sided incision. The cavity is divided into a large right-sided posterior chamber (PV) and a smaller left-sided chamber by an oblique septum. We believe this septum to be the bulboventricular septum (BVS). The valve taking blood from the left atrium straddles this septum and has the appearance of a morphological tricuspid valve (LAVV). Note the multiple posterior papillary muscles arising from the primitive ventricle, and the single anterior muscle from the outlet chamber tethering the anterior cusp (see D). The pulmonary artery arises from the primitive ventricle and there is pulmonary-tricuspid valvar fibrous continuity. (D) Ventricular morphology as seen through the left-hand incision. The small anterior outlet chamber is left sided but its outlet portion sweeps to the right to give rise to the right-sided aorta. Note the prominent anterior papillary muscle (APM) straddling the bulboventricular septum. Despite the fact that the left-sided valve present has the appearance of a tricuspid valve, in functional terms this heart has right atrial orificial atresia and is comparable to the hearts illustrated in the previous figures.*

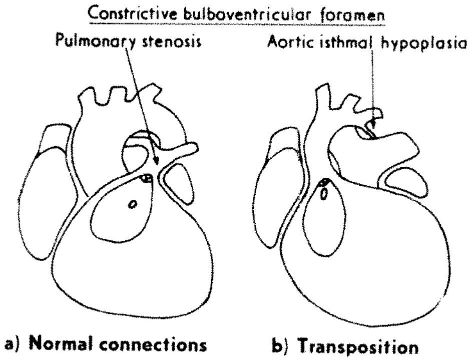

Constrictive bulboventricular foramen
Pulmonary stenosis
Aortic isthmal hypoplasia
a) Normal connections
b) Transposition

Fig. 14 *Diagram showing that the physiological consequences of bulboventricular construction depend upon ventriculoarterial connections. When the arteries are normally connected, pulmonary stenosis will be produced. In the presence of transposition, aortic stenosis will ensue with the likely sequel of aortic isthmal hypoplasia.*

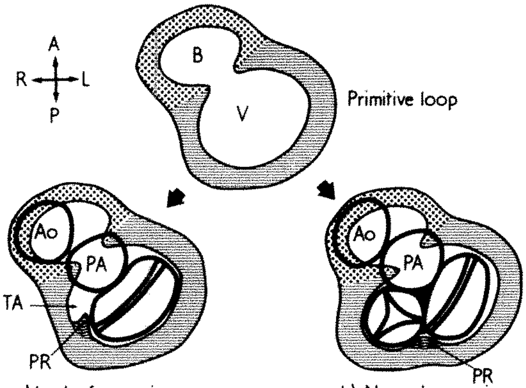
Rao *et al.*, 1973) that there is considerable variation in ventricular morphology in hearts with atresia of the right atrioventricular orifice. Furthermore, as shown by both Henry and Danielson (1974) and Quero-Jimenez *et al.* (1975) there are further variations in ventriculoarterial connections than merely 'normal relations' or 'transposition'. The question is then posed as to how all these variations can best be described. We believe that adequate description and classification can only be produced by use of the segmental approach (Van Praagh, 1972; Shinebourne *et al.*, 1976). However, it became evident that application of such a segmental approach gave rise to many potential controversies.

A. WHY RIGHT ATRIOVENTRICULAR ORIFICIAL ATRESIA RATHER THAN TRICUSPID ATRESIA?

In this investigation we have described hearts in which the right atrial chamber was blind ending. In all but 2 of these hearts the valve present between the left atrium and the ventricular chamber was a morphologically mitral valve. However, in the 2 remaining hearts the left-sided valve bore more resemblance to a morphologically tricuspid valve. The morphological inference to be drawn from this information is that d-bulboventricular looping occurred in all but the 2 hearts with left-sided tricuspid valves, in which l-looping is presumed to have occurred. Would it not therefore be more accurate to separate these 2 hearts as *mitral* atresia? Morphologically this would be completely acceptable. However, we submit that in clinical terms the important feature is that the right atrium is blind ending, irrespective of whether the atretic valve is morphologically mitral or tricuspid. Furthermore, we believe that it would not be possible angiographically to distinguish a mitral valve from a tricuspid valve. The clinical evidence for l-looping would be inferential, being deduced from presence of a left-sided outlet chamber. Yet one of the hearts presently studied (Fig. 12) possessed a left-sided outlet chamber supporting an l-transposed aorta; these observations suggest l-looping but the left atrioventricular valve was morphologically a mitral valve. We, therefore, consider it more accurate and less confusing to refer to 'right atrioventricular orificial atresia' (or 'right atrial orificial atresia'). We have thus excluded from this series hearts with evidence of l-bulboventricular looping and left atrial orificial atresia. In morphological terms this condition represents 'tricuspid atresia' (Harris and Farber, 1939; Keith *et al.*, 1958), but we prefer to consider it as left atrioventricular orificial atresia, and we would group it together with other forms of primitive ventricle which exhibit blind-ending left atria (Quero, 1970; Macartney *et al.*, 1976).

B. CAN RIGHT ATRIOVENTRICULAR ATRESIA COEXIST WITH PRIMITIVE VENTRICLE?

As Macartney and his colleagues (1976) have recently indicated, it has become customary to exclude by definition from the category of primitive (single or common) ventricle, cases of atrioventricular valve atresia. They concluded that in terms of angiography this exclusion was unjustified, a view previously put forward by Quero (1970). Our investigation fully endorses their opinions, and shows that the majority *but not all* of our examples of right atrioventricular valve atresia are more akin to primitive ventricle than to hearts with normal right and left ventricles. Van Praagh *et al.* (1964) did not expand on their reasons for excluding cases with atrioventricular valve atresia from single ventricle. Lev and his colleagues (1969) believed that the differentiation depended on whether the main chamber contained the undeveloped right ventricular inflow portion in a position in which it was related to the atretic orifice. They conceded the possibility that this might indeed be the case in hearts with transposition, as previously suggested by Edwards *et al.* (1965). However, they stated that this was not the case with normally connected arteries, citing as evidence the fact that conducting tissue studies had demonstrated a right bundle-branch entering the outlet chamber. Our own histological observations are in agreement with theirs, but our interpretation differs. We have observed a similar distribution of conducting tissues in the outlet chamber in primitive (single) ventricle (Anderson *et al.*, 1974a). Furthermore, our histological studies in right atrioventricular orificial atresia have shown that the atretic orifice does indeed 'point' to the main chamber. This fact indicates to us that the hearts thus fulfil the criterion demanded by Lev *et al.* for single ventricle, since we believe that the right ventricular inflow portion is indeed contained within the main chamber, which therefore constitutes a primitive ventricle. As in 'single' or 'common' ventricle with outlet chamber, the outlet chamber represents the embryonic bulbus (Keith, 1906). We suggest that in primitive ventricle with two atrioventricular valves, the right inflow portion has developed with persistence of the bulboventricular septum in its initial anterior position, whereas in right atrioventricular orificial atresia there has been lack of development of the inflow portion but persistence of the anteriorly situated bulboventricular septum (Fig. 15). This concept is supported by the previous study of Rosenquist *et al.* (1970), who showed most elegantly that the atretic right atrioventricular orifice was potentially in communication with the 'left' ventricle rather than the 'right'. In view of this evidence, it seems to us proper that the definition of primitive (single or common) ventricle should be modified as suggested by Macartney *et al.* (1976). Thus, if primitive ventricle exists when both atria are either actually or *potentially* in communication with the same ventricular chamber, then the majority of specimens of right atrioventricular valve atresia can properly be classified as primitive ventricle (Anderson *et al.*, 1976).



a) Lack of expansion b) Normal expansion

Fig. 15 *Diagrams illustrating the morphogenetic link between primitive ventricle with outlet chamber and two atrioventricular valves (lower right hand diagram) and primitive ventricle with outlet chamber and right atrial orificial atresia (lower left hand diagram). Both represent persistence of that stage of development where the bulbus (outlet chamber: B) is separated from the primitive ventricle (main chamber: V) by the bulvoventricular septum. In primitive ventricle with right atrial orificial atresia, it can be hypothesised that there has been failure of development of the inflow tract of the right ventricle, derived from the primitive ventricle. In primitive ventricle with two atrioventricular valves, the right ventricular inflow tract is developed, but is separated from the outlet chamber (bulbus) by the persistent bulboventricular septum. (Reproduced from Anderson* et al., British Heart Journal, **38**, *558, 1976.)*

It must be emphasised once more that not *all* cases of right atrioventricular orificial atresia are cases of primitive ventricle. Six of our cases had true right ventricles. Four of these had right ventricular hypoplasia, comparable with the cases reported by Okin *et al.* (1969). The remaining cases had imperforate Ebstein's anomaly of the right atrioventricular valve. This rare condition was well documented by Rao *et al.* (1973) who reviewed previous cases and emphasised the clinical importance of its recognition.

C. ASSOCIATED ANOMALIES

The clinical importance of the classification of Edwards and Burchell (1949) was that it described the state of pulmonary blood flow. In order to convey this important information, Henry and Danielson (1974) tabulated their extensive findings, using a modification of this approach. However, the segmental approach does not preclude the provision of this information if it is appreciated that pulmonary stenosis is an associated anomaly. An important and vital part of segmental nomenclature is the tabulation of additional anomalies. In this way other information will also be transmitted and attention focused on the genesis of these associated anomalies. Thus pulmonary stenosis with right atrioventricular orificial atresia is most frequently the result of a constrictive bulboventricular foramen. If one thinks segmentally it is readily apparent that a similar constriction in the presence of transposition will result in aortic stenosis and associated isthmal hypoplasia. When pulmonary stenosis occurs with transposition, it must have a different cause, usually posterior deviation of the infundibular septum.

D. SURGICAL SIGNIFICANCE

With the demonstration by Fontan and Baudet (1971) that radical palliative surgery is possible in the presence of right atrial orificial atresia, knowledge of all aspects of anatomy is vital. It will immediately be evident that hearts with formed right ventricles do not require a Fontan-type procedure. In one of the hearts we have described, excision of an imperforate Ebstein anomaly would have restored the normal circulatory pattern (Fig. 6). Rao *et al.* (1973) have previously commented on the surgical importance of recognising this variety of right atrial orificial atresia. It is because of the surgical implications that we have excluded from this series hearts with left atrial orificial atresia even when the atretic valve was morphologically tricuspid. Since the Fontan operation can be employed only when the *right* atrium is blind ending, we prefer to distinguish between right and left atrial orificial atresia, rather than between tricuspid and mitral atresia.

The fact that a small number of the hearts were examples of primitive ventricle *without* outlet chamber may also be significant. It is becoming customary now to insert the distal end of the right atrial conduit to the outlet chamber. Clearly this would be impossible when an outlet chamber is not present. In the hearts we studied an outlet chamber was also effectively lacking when there was pulmonary atresia with normal ventriculoarterial connections. However, in all other hearts a good size outlet chamber was present even when secondary constriction of the bulboventricular foramen had occurred. In 4 hearts a second constriction was present distally within the outlet chamber which may have detracted from its functional value as a potential pumping chamber if the distal end of the conduit had been inserted to that chamber.

The type of ventriculoarterial connection present also influences the site of insertion of the distal end of the conduit. The outlet chamber can only be employed as part of the pulmonary circuit in the presence of normally connected arteries. It is important to realise, therefore, that normal ventriculoarterial connections can exist with an anterior left-sided aorta. This relation is usually termed anatomically corrected malposition, and its association with right atrial orificial atresia has previously been stressed by Melhuish and Van Praagh (1968) and by Freedom and Harrington (1974). It must also be remembered that any possible ventriculoarterial connection can exist with right atrial orificial atresia.

Conclusions

In summary, therefore, we believe that our study has shown a basic subdivision in terms of ventricular morphology in hearts with atresia of the right atrioventricular orifice, the majority being examples of primitive ventricle with outlet chamber. We believe that understanding of the condition is enhanced if the anomaly is described as right atrial orificial atresia rather than 'tricuspid atresia' since in some hearts the atretic orifice may be a mitral orifice, but nevertheless its effect is to shunt systemic venous return to the left atrium. Finally, we believe that our investigation endorses once more the value of a segmental approach to diagnosis (Van Praagh, 1972; Shinebourne *et al.,* 1976), since many variants of right atrial orificial atresia are described, while others probably exist which have yet to be described.

We are indebted to all our clinical colleagues for permission to study hearts from patients previously in their care. We are also indebted to colleagues who placed their specimens at our disposal, in particular Drs. J. Van Gorp and Sj. Sc. Wagenaar of Utrecht and Dr. Oppenheimer-Decker of Leiden. We were greatly assisted in the final preparation of the manuscript and illustrations by Miss N. de Freitas and Mrs. S. Y. Ho.

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The left ventricle in congenital isolated pulmonary valve stenosis
A morphological study

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The wall thickness of the left ventricle was measured in the hearts of 16 children and 2 adults who died of congenital pulmonary valve stenosis. A right-to-left shunt through a patent foramen ovale had existed in 12 cases and was excluded in the other 6. The thickness of the left ventricular wall and the interventricular septum was increased in the majority of hearts, especially in the older patients. There was a good correlation between wall thickness and histological appearance of the left ventricular myocardium; in 2 cases there was also evidence of left ventricular myocardial fibrosis. The coronary arteries appeared normal in all cases. A direct interaction between the ventricles was thought to be a possible mechanism.

Congenital pulmonary valve stenosis with intact ventricular septum is usually regarded as a lesion affecting only the right side of the heart. However, haemodynamic studies with isolated heart preparations of animals have shown that augmentation of the right ventricular load has an unfavourable influence on the performance of the left ventricle (Henderson and Prince, 1914; Bucher and Von Capeller, 1954; Ullrich *et al.*, 1954; Moulopoulos *et al.*, 1965; Urschel *et al.*, 1971; Elzinga, 1972; Elzinga *et al.*, 1974; Harinck, 1974; Versprille *et al.*, 1974). Moreover, sustained augmentation of the right ventricular load by banding of the main pulmonary artery in dogs will ultimately lead to hypertrophy of the left ventricle (Laks *et al.*, 1969, 1972).

It is surprising, therefore, that little is known about the left ventricle in patients with isolated congenital pulmonary valve stenosis. As this information is of clinical importance, a morphological study of human hearts with isolated pulmonary valve stenosis, with particular emphasis on the occurrence of pathological changes in the left ventricle, was undertaken.

Subjects and methods

The hearts from 18 patients, aged 3 days to 26 years, were examined. All had congenital pulmonary valve stenosis, with or without an open foramen ovale but with no cardiac or other lesion that could have interfered with the function of the left ventricle.

Four patients died without an operation; in the other 14 pulmonary valvotomy had been carried out, and death had followed shortly afterwards in all but one patient who died 4 years later. In 12 cases a right-to-left shunt through an open foramen ovale had been present before death, in the other 6 the presence of a shunt had been excluded. The hearts were fixed in 80 per cent alcohol to which some glycerin had been added.

MACROSCOPICAL EXAMINATION

Wall thickness was measured as described by Lev *et al.* (1961) and Rowlatt *et al.* (1963), in the right ventricle 0·5 to 1·0 cm below the pulmonary orifice (RV-P), and in the left ventricle at its maximum thickness (LV-M). The maximal thickness of the interventricular septum (IVS-M) was measured from a cut perpendicular to the axis of the heart. Trabeculae were excluded in all measurements.

Because values for ventricular wall thickness of

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normal hearts fixed as described above were not available, the values for normal hearts fixed in formaldehyde (Rowlatt *et al.*, 1963) were used. Before a comparison was made between the values obtained from our own study and these reference values, the influence of the different fixation fluids on ventricular wall thickness was investigated with transverse sections of pig hearts. The thickness of the lateral wall of the left ventricle and of the interventricular septum were measured before and after fixation in 80 per cent alcohol or formaldehyde. After a fixation period of 3 months there was no significant difference between these two methods of fixation. If we accept that human hearts do not differ in this respect from pig hearts, the values for wall thickness in our study may be compared with the normal values of Rowlatt *et al.* (1963).

MICROSCOPICAL EXAMINATION

In 16 of the 18 hearts a microscopical study could be performed. The sections were taken from the sites used for the measurements of wall thickness. The diameter of the myocardial cells was measured using an ocular micrometer. A total number of 50 measurements was taken in each case, for both right and left ventricular myocardium. An average fibre diameter was then calculated.

Fibrosis was defined as an increase of connective tissue. The presence of fibrosis was graded in a semiquantitative manner, as follows: a slight increase was graded as + (Fig. 1A) and a greater increase as ++ (Fig. 1B).

Particular attention was also given to myocardial fibre arrangement and to the intramural coronary arteries.

Results

MACROSCOPICAL APPEARANCES

On inspection of the specimens right ventricular

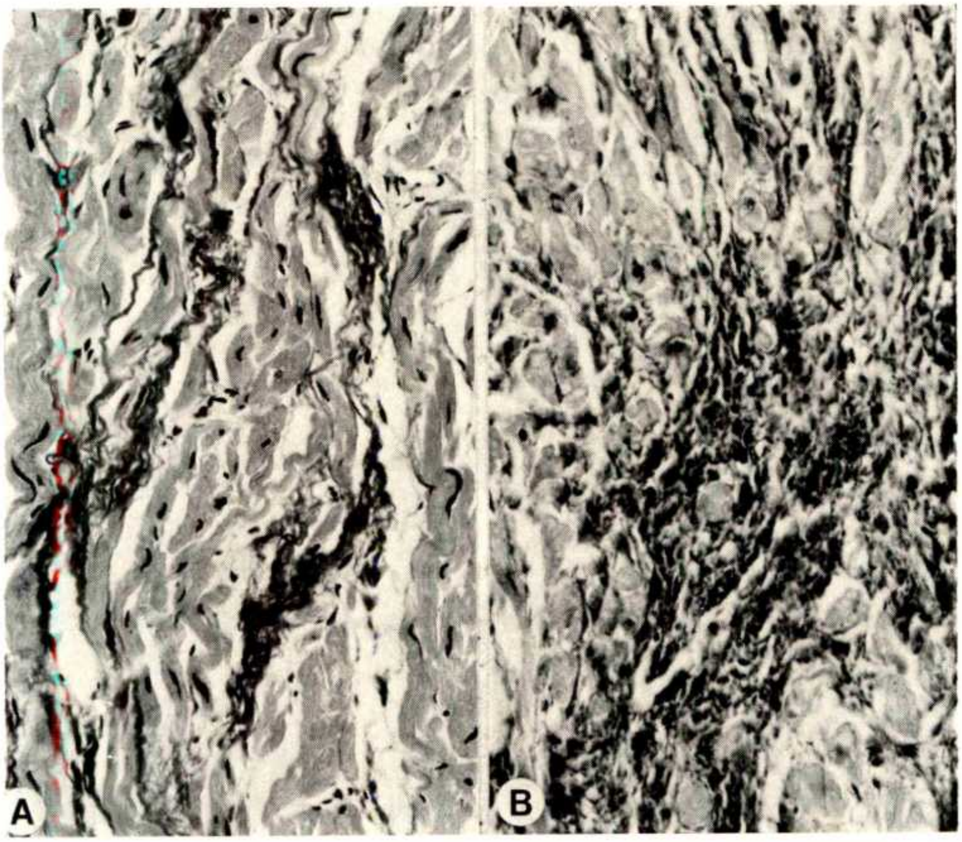

Fig. 1 *Histological sections of right ventricular myocardium to show fibrosis. (A) shows slight fibrosis, indicated as +; (B) shows conspicuous fibrosis indicated by ++. (Elastic van Gieson ×170.)*

hypertrophy was a constant feature in all cases. Moreover, gross inspection, particularly in the older hearts, also showed that there was an increase in wall thickness of the left ventricle in the majority of those hearts studied (Fig. 2 and 3). The results of measurement of the ventricular wall thickness are compared with the normal values in the paediatric age group in Fig. 4. The values for right ventricular wall thickness (RV-P) are plotted against age from birth, and those for maximal thickness of the left ventricular wall (LV-M) are plotted against age from conception; this method was that used by Rowlatt *et al.* (1963). The values for right ventricular wall thickness are all above the 95th centile of the reference values. The values for maximal left ventricular wall thickness in the older children are mostly on or above the 95th centile.

When the relation between left ventricular wall thickness and body weight is plotted (Fig. 5) the values for maximal thickness of the left ventricle exceed the 95th centile in all children of 10 kg or more. The LV-M value of the 13-year-old boy is not shown as his body weight just before death is unknown. In the majority of patients the body weights were in accordance with their ages and heights; 2 cases were even robust.

The results of the macroscopical investigation of the two adults are shown in Table 1. The wall thickness of both right and left ventricle of the 25-year-old man was above normal. The wall thickness of the right ventricle in the 26-year-old women was considerably increased, and though the left ventricle appeared large its wall thickness was within normal limits; however, the microscopical appearance (see Table 2) indicated left ventricular hypertrophy. Fig. 6 shows that there is a positive

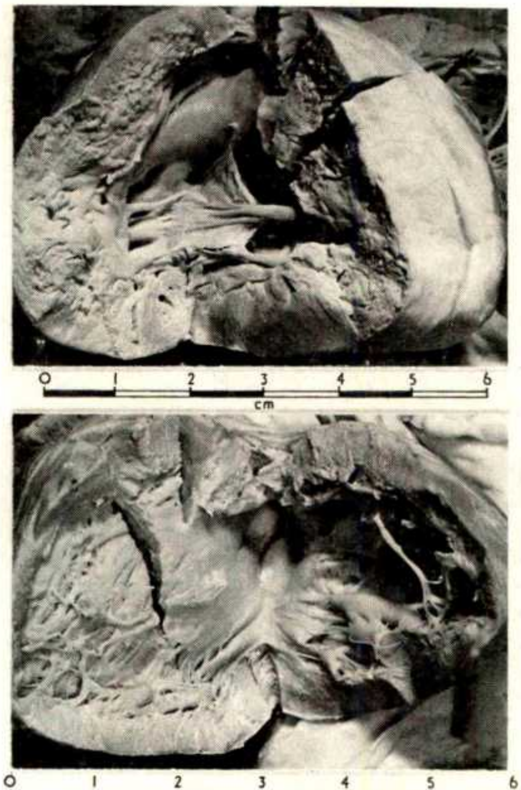

Fig. 2 *View of opened sinus part and outflow tract of the right ventricle (above), with distinct hypertrophy of the wall. The opened left ventricle (below), with the septum on the left, shows no increase in wall thickness. A right-to-left shunt had existed through an open foramen ovale in this patient, age 14 months (23 from conception), bodyweight 8·4 kg.*

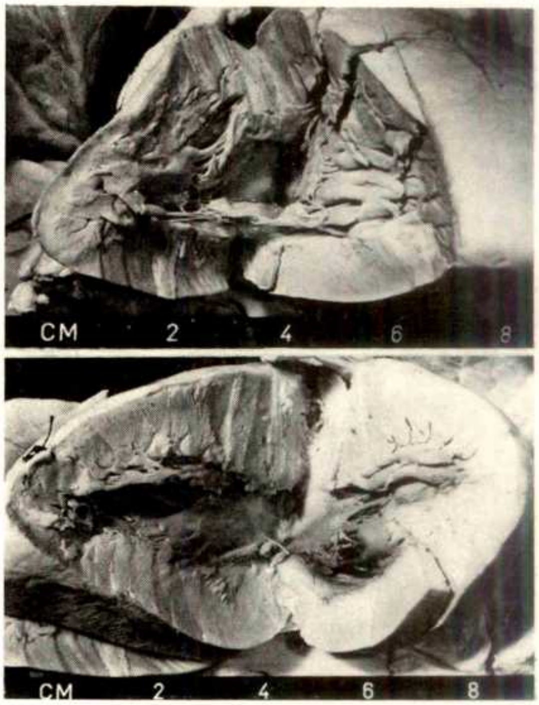

Fig. 3 *View of opened right ventricle (above), to show pronounced right ventricular hypertrophy. The opened left ventricle (below) also shows considerable hypertrophy of its wall. In this patient no right-to-left shunt had existed; age 9¼ years (10 from conception), bodyweight 22·6 kg.*

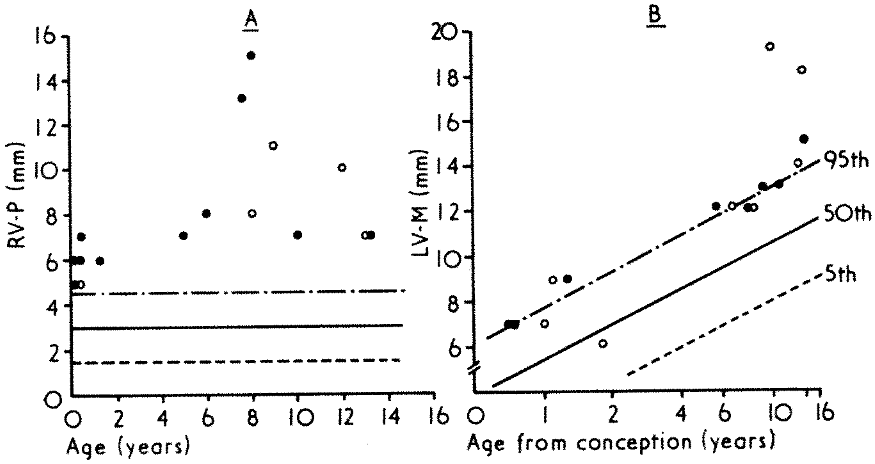

Fig. 4 *Wall thickness of the right and left ventricle in the different age groups. The normal values according to Rowlatt* et al. *(1963) are represented in centiles as follows - - - 5th, — 50th, —·— 95th. The closed dots represent the patients with a right-to-left shunt through an open foramen ovale, the open circles without shunt. Abbreviations as in Table 1.*

correlation between the maximal thickness of the left ventricular wall (LV-M) and the maximal thickness of the interventricular septum (IVS-M).

MICROSCOPICAL APPEARANCES

The histological findings are summarised in Table 2. The assessment of whether or not there was hypertrophy was based mainly upon personal experience. Under 1 year of age an average fibre diameter of less than 5 μ is considered normal. In the age group from 1 to 10 years a diameter of less than 10 μ is considered normal. These figures apply to myocardium of both right and left ventricles. In the age group from 10 to 20 years an average fibre diameter of less than 10 μ is considered normal for the right ventricle, and of less than 15 μ for the left ventricle. When these figures are taken into account it is seen that 15 of the 16 hearts examined histologically showed evidence of right ventricular hypertrophy; the only heart without histological evidence of right ventricular myocardial hypertrophy was that of the 14-day-old infant.

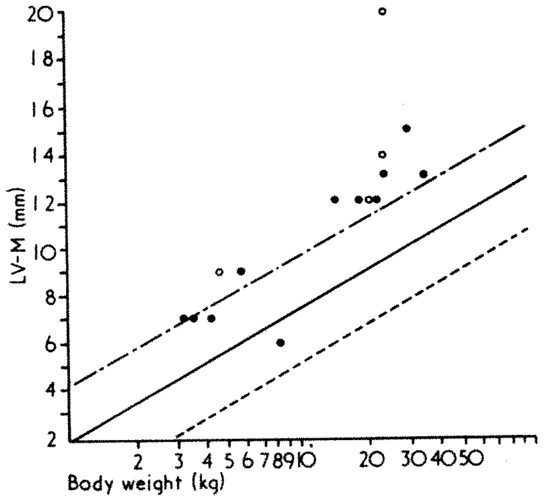

Fig. 5 *The relation between wall thickness of the left ventricle and bodyweight. The normal values according to Rowlatt* et al. *(1963) are represented in centiles as follows - - - 5th, — 50th, —·— 95th. The closed dots represent the patients with a right-to-left shunt through an open foramen ovale, the open circles those with no shunt. Abbrevations as in Table 1.*

Evidence for left ventricular hypertrophy was found in 10 of the 16 hearts studied; there was a definite tendency for this to be seen in the older patients.

Fibrosis of the right ventricular myocardium appeared in 8 cases and always accompanied an increase in right ventricular wall thickness. The left ventricular myocardium showed fibrosis of moderate degree in 3 cases, each with pronounced left ventricular hypertrophy. Apart from the hypertrophic changes, no other abnormalities of the myocardium

Table 1 *Macroscopical findings in 2 adults*

Sex	*Age (y)*	*RV-P*	*LV-M*	*IVS-M*
M	25	9	17	16
F	26	16	12	12

Measurements are given in millimetres.
RV-P, right ventricular wall thickness; LV-M, maximal wall thickness of the left ventricle; IVS-M, maximal thickness of the interventricular septum.

Table 2 *Microscopical features of myocardium of right and left ventricles*

Age	*Sex*	*Right ventricle*			*Left ventricle*		
		Myocardial fibre diameter (μ)		*Fibrosis*	*Myocardial fibre diameter (μ)*		*Fibrosis*
3d	M						
14d	F	2·5	(—)	—	2·5	(—)	—
3m	F	7·5	(+)	—	5	(—)	—
4½m	M	7·5	(+)	+	7·5	(+)	—
5½m	M	7·5	(+)	—	7·5	(+)	—
14m	F	12·5	(+)	+	5	(—)	—
5y	F	12·5	(+)	+	7·5	(—)	—
6y	F	15	(+)	—	7·5	(—)	—
7½y	F	12·5	(+)	++	10	(+)	—
8y	M	15	(+)	++	15	(+)	+
8y	M	15	(+)	++	10	(+)	—
9y	M	15	(+)	—	12·5	(+)	—
10y	F	15	(+)	—	12·5	(+)	—
12y	M	12·5	(+)	—	10	(—)	—
13y	F	12·5	(+)	—	15	(+)	—
13y	M	15	(+)	+	12·5	(+)	+
25y	M						
26y	F	20	(+)	+	25	(+)	+

The interpretation of the average fibre diameter is shown in brackets: (+), hypertrophy; (—), no hypertrophy. Fibrosis is indicated by —, absent; +, mild; ++, severe.

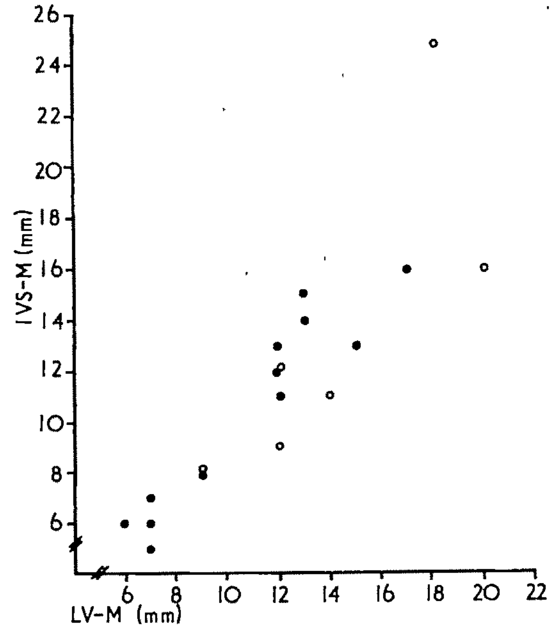

Fig. 6 *The relation of the maximal thickness of the interventricular septum (IVS-M) and of the maximal thickness of the lateral wall of the left ventricle (LV-M). r=0·87. The closed dots represent the patients with a right-to-left shunt through an open foramen ovale, the open circles without shunt.*

were noted. The intramural branches of the coronary arteries appeared normal in every instance. Slight alterations in wall structure were occasionally seen in arterial branches coursing through areas of fibrosis.

Discussion

This study has shown that left ventricular hypertrophy may be present in patients with isolated pulmonary valve stenosis. However, it should be stated that ventricular wall thickness as a guide to the presence of hypertrophy has the disadvantage that false negative results may occur because of dilatation. It follows that cases with increased ventricular wall thickness may have been missed, but even so half the cases presented had LV-M values above the 95 per cent confidence limits when LV-M was plotted against age (Fig. 4). Moreover, we feel confident that left ventricular hypertrophy does occur, since 10 of the 16 hearts studied histologically showed evidence of left ventricular hypertrophy. This finding suggests that the condition of congenital pulmonary valve stenosis is one that affects not only the right side of the heart. The mechanisms that underlie the appearance of left ventricular hypertrophy are still a matter of dispute. The phenomenon cannot simply be attributed to the degree of hypertrophy of the right ventricle since no positive correlation between the LV-M and RV-P values was found. Experimental studies with animals have shown that an increase in the afterload of the right ventricle, produced by banding the main pulmonary artery, results in right ventricular hypertrophy within a few days (Spann *et al.*, 1967; Archie *et al.*, 1974), though hypertrophy of the left ventricle does not become manifest until some months later (Laks *et al.*, 1969, 1972; Harinck, 1974). Apparently a time factor is of importance, since hearts of younger infants in our series showed less left ventricular hypertrophy than those of older children, or none at all. Keith and coworkers (1967) have stated that hypertrophy of the left ventricle is seen only in patients with severe pulmonary stenosis. On the other hand, Herbert and Yellin (1969) were unable to confirm this, finding abnormally high left ventricular end-diastolic pressures in patients with even a mild to moderate pulmonary stenosis.

Although histological examination of the hearts in our series showed only hypertrophy with normal looking coronary arteries, Beçu *et al.* (1976) have reported a bizarre arrangement of left ventricular muscle fibres and involvement of coronary vessels.

It has been suggested that myocardial hypoxia is a factor in the development of left ventricular hypertrophy, particularly in patients with a right-to-left shunt through a patent foramen ovale. Increased blood viscosity from concomitant polycythaemia, secondary to this shunt, may be an additional factor. However, left ventricular hypertrophy was not confined to cases in our series with a right-to-left shunt, but occurred also in patients without a shunt; furthermore, the left ventricular hypertrophy was not more pronounced in the hearts with a right-to-left shunt than in those without.

In acute haemodynamic studies in animals it was shown that coronary blood flow diminished when the afterload of the right ventricle was raised (Elzinga, 1972; Harinck, 1974). This phenomenon may be an additional possible cause of myocardial hypoxia. However, it has also been shown that coronary blood flow adapts to a sustained increase in right ventricular afterload (Archie *et al.*, 1974).

Anatomical continuity of the musculature between right and left ventricles has been suggested as a possible cause for the development of left ventricular hypertrophy in patients with chronic lung disease (Rao *et al.*, 1968). Sustained stress to the right ventricle may then lead to abnormalities in the left ventricle. However, if this were true, one might also expect the reverse to take place, with sustained stress to the left ventricle directly influencing the right; such an effect, as far as we know, has never been described. Nevertheless, the possibility of a direct interaction between the ventricles cannot be ruled out.

It is suggested that changes occurring on the right side of the heart result in altered left ventricular geometry. Increase in afterload of the right ventricle results in an increase in right ventricular end-diastolic volume, which may flatten the globular or egg-shaped left ventricle (Harinck, 1974; Versprille *et al.*, 1974) which then has a less favourable shape for the development of pressure. In fact, changes in geometry of the left ventricle induced by alterations in right ventricular load have been reported by Urschel *et al.* (1971) and by Bemis *et al.* (1974). These investigators showed that an acute constriction of the main pulmonary artery in dogs causes an increase in the anteroposterior diameter of the left ventricle and a reduction of the septum to free wall diameter. Thus, the radius of the lateral wall of the left ventricle is enlarged. According to the modified Laplace equation,[1] this part of the left ventricle has to produce more tension (and thus work) to maintain a given stroke volume at a given aortic pressure. Sustained increased tension may lead eventually to hypertrophy. In our opinion, this mechanism could be of prime importance in the pathogenesis of the left ventricular hypertrophy.

It is also interesting to note than prolonged and pronounced hypertrophy of myocardium subsequently leads to fibrosis, a feature well known from other pathological conditions.

Indeed, right ventricular fibrosis was a frequent feature in our series. Three of the older children, with pronounced left ventricular hypertrophy, also presented features of fibrosis in the left ventricular myocardium. Obviously such alterations will affect myocardial function, though a considerable lapse of time is needed. These anatomical findings further endorse the impression that problems may arise from the left ventricular myocardium in patients with isolated valve pulmonary stenosis, primarily a malformation confined to the right heart.

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[1] $T = PR/2d$, where T = tension, P = pressure, R = radius, and d = wall thickness.

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Total anomalous pulmonary venous drainage in infancy[1]

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Between May 1971 and December 1975, 39 infants had operations for correction of total anomalous pulmonary venous drainage. Fourteen of the 39 patients were under 1 month of age at the time of operation. Twenty-four patients had supracardiac, 7 intracardiac, and 6 infracardiac total anomalous pulmonary venous drainage, and 2 had a mixed type. The overall hospital mortality was 36 per cent. There have been no late deaths. The improvement in survival rate in this series is attributed to: (1) earlier recognition and prompt referral, (2) an aggressive approach to diagnosis involving complete cardiac catheterisation and angiocardiography, (3) vigorous preoperative care, (4) early complete correction including construction of a large anastomosis and enlargement of the left atrium when indicated, and (5) intensive postoperative management paying particular attention to fluid balance and treatment of pulmonary complications. Operative mortality was highest in patients with total anomalous pulmonary venous drainage directly to the superior vena cava, and in those with infradiaphragmatic drainage of whom all had pulmonary venous obstruction. Mortality was not closely related to age, body weight, or severity of pulmonary hypertension.

Total anomalous pulmonary venous drainage was first described by Friedkowsky in 1868 (Brody, 1942). It was not, however, until 1942 when Brody reported 37 cases that it became a recognised clinical entity (Brody, 1942). The incidence of total anomalous pulmonary venous drainage is approximately 1·5 per cent of children born with congenital heart disease (Keith *et al.*, 1967).

The majority of patients with total anomalous pulmonary venous drainage have symptoms during the first year of life (Gathman and Nadas, 1970). The few who remain asymptomatic have a relatively good prognosis and operation can be performed electively later in childhood at low risk (Gomes *et al.*, 1970). Eighty per cent of symptomatic infants, if left untreated, will die before they reach their first birthday (Bonham-Carter *et al.*, 1969).

Medical treatment consisting of antifailure therapy may be beneficial, but in the presence of pulmonary venous obstruction and/or pulmonary hypertension, does not improve survival rate (Gathman and Nadas, 1970). Palliation by balloon atrial septostomy has been tried (Miller *et al.*, 1967; El-Said *et al.*, 1972), but is helpful only in the few cases where the obstruction to pulmonary venous return is produced by a small foramen ovale.

The first attempt to correct total anomalous pulmonary venous drainage surgically was made by Muller in 1950, who anastomosed the left atrium to the common pulmonary venous channel (Muller, 1951). A semi-open atrial well technique was tried by Burroughs and Kirklin in 1954 (Burroughs and Kirklin, 1956). In 1955, Lewis performed a total correction using hypothermia with inflow occlusion which was successful in a 5-year-old patient (Lewis *et al.*, 1956). In 1957, Cooley performed a successful correction of total anomalous pulmonary venous drainage using cardiopulmonary bypass (Cooley and Ochsner, 1957).

In older children, total correction of anomalous pulmonary venous drainage has been performed successfully, with the use of cardiopulmonary bypass, for several years. Before 1970, however, mortality rates for infants less than 1 year of age remained high (Mustard *et al.*, 1962; Leachman *et et.*, 1969; Gomes *et al.*, 1970; Behrendt *et al.*, 1972; Wukasch *et al.*, 1975). With improved techniques for open cardiac repair in early infancy, the mortality rates for this group have fallen in the past five

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Table 1 *Total anomalous pulmonary venous drainage in 86 infants*

Period	*Number*	*Survived*
1963–1970	47	15 (32%)
1971–1975	39	25 (64%)

years (Lemoine, 1975; Barratt-Boyes, 1973; Applebaum *et al.*, 1975; W. M. Gersony, F. O. Bowman, and J. R. Malm, 1975, personal communication). In this unit the operative mortality for total anomalous pulmonary venous drainage in infancy has decreased from 68 per cent in 1963 to 1970 to 36 per cent in 1971 to 1975 (Table 1).

Clinical diagnosis

Infants with total anomalous pulmonary venous drainage may present with signs of heart failure and/or cyanosis. The development of severe heart failure is often rapid: cyanosis is usually moderate on examination. Peripheral pulses are poor. Tachypnoea, tachycardia, gallop rhythm, and enlarged liver complete the picture of heart failure. On auscultation there are usually no murmurs. A closely split second sound may be a clue to the diagnosis.

The appearances on the chest *x*-ray film depend on the type of total anomalous pulmonary venous drainage and its physiological consequences. When there is no obstruction to pulmonary venous return, the heart tends to be large and the pulmonary vascularity is increased. If the pulmonary venous return is obstructed, the heart is usually not enlarged and the lungs are oedematous because of pulmonary venous hypertension; indeed, the combination of a heart which is not enlarged and pulmonary oedema is characteristic of obstructed total anomalous pulmonary venous drainage, though it also occurs in cor triatriatum. In younger infants, pulmonary oedema is localised to the perihilar regions, with septal lines often visible in the retrosternal space or costophrenic angles. Pulmonary oedema must be distinguished from hyaline membrane disease where the changes are usually diffused throughout all lung areas. In later infancy when total anomalous pulmonary venous drainage is to the left innominate vein or to the right superior vena cava the diagnosis may be suspected from widening of the upper mediastinal shadow.

The electrocardiogram shows right axis deviation, and right ventricular hypertrophy is a constant feature; right atrial hypertrophy usually develops during the first 3 months of life and is therefore uncommon in the neonatal period.

The presence of pulmonary oedema, enlarged liver, and a normal sized heart in a sick, slightly cyanosed baby is very suggestive of obstructed total anomalous pulmonary venous drainage. When the diagnosis is suspected, the infant should be transferred immediately to a specialised unit, where cardiac catheterisation and angiocardiography can be performed on an emergency basis. We believe that it is safer to investigate more infants suspected of having an obstructed total anomalous pulmonary venous drainage rather than to miss the diagnosis and lose the patient.

DEFINITIVE INVESTIGATION

The importance of complete cardiac catheterisation and of high quality selective angiocardiograms cannot be overemphasised. It is important to outline the drainage from both lungs clearly so that the mixed type of total anomalous pulmonary venous drainage is not overlooked and the presence of pulmonary venous obstruction recognised. It is equally important to exclude additional cardiac malformations particularly persistent ductus arteriosus, ventricular septal defect, and coarctation of the aorta. If these are present, they should be corrected at the time of operation for redirection of pulmonary venous inflow.

PREOPERATIVE MANAGEMENT

Intensive supportive care is of utmost importance to neonates and small infants with total anomalous pulmonary venous drainage. We believe that all the techniques used in intensive care should be administered from the time the diagnosis is suspected, through transport, investigation, operation, and postoperative recovery, if circumstances warrant such measures. Insertion of arterial and central venous catheters is essential if arterial blood pressure, central venous pressure, and arterial blood gases are to be monitored. A central venous line is also useful for the administration of drugs, including sodium bicarbonate, calcium, and catecholamines, if required. A urinary catheter is inserted. The baby's temperature is controlled in an incubator or with an infrared warmer. All metabolic imbalances are corrected. Oxygen should be administered, and if hypercapnia or respiratory distress is present, the child should be intubated and ventilated. Though these measures are not always necessary, the use of some or all of these techniques in the preoperative period will allow transport and time for the adequate investigation of extremely ill infants.

Table 2 *Clinical values in 39 infants, 1971 to 1975*

	Range	*Mean*
Age at operation (d)	1–352	83
Body weight at operation (kg)	2·6–6·4	4·0
Arterial O_2 saturation (%)	33–92	75
Pulmonary/systemic systolic pressure ratio	0·27–1·83	0·98
PV to RA mean gradient (mmHg) (17 patients)	0–34	11

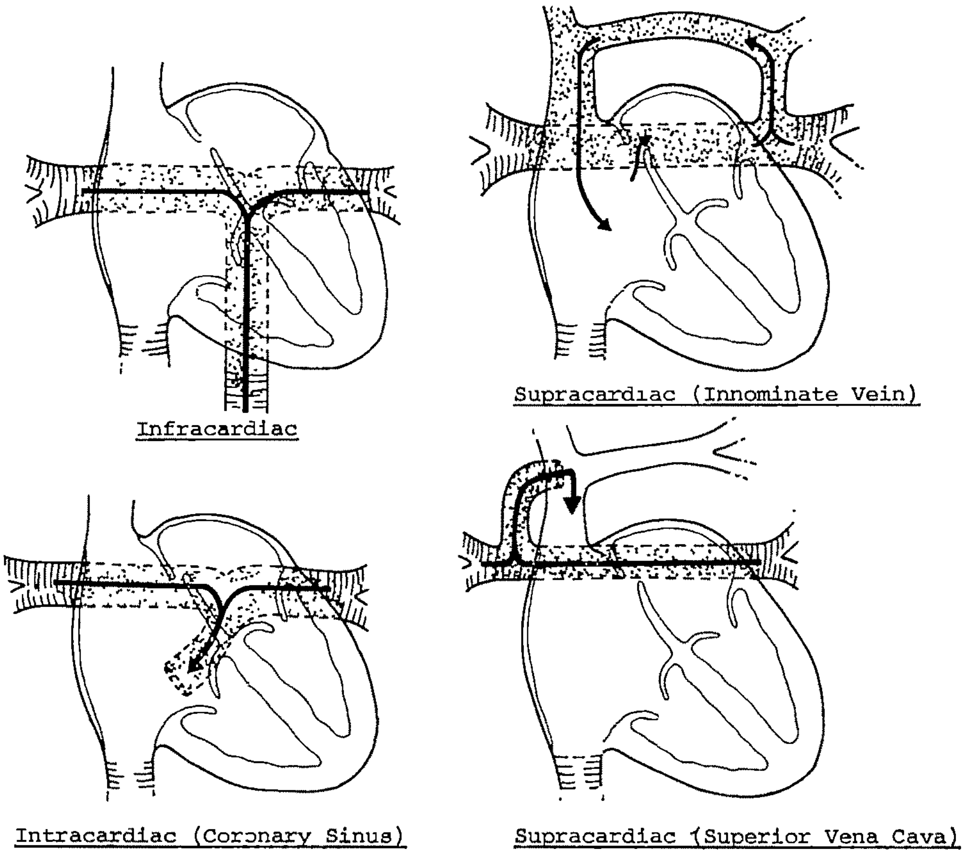
Patients

Thirty-nine infants had operations for correction of total anomalous pulmonary venous drainage between May 1971 and December 1975. The age of the infants at the time of operation ranged from 1 day to 352 days (mean 83 days). The weight at the time of operation ranged from 2·6 kg to 6·4 kg (mean 4·00 kg). Twenty-six were boys and 13 girls. All infants were symptomatic and 31 had a pulmonary arterial systolic pressure which was more than 60 per cent of the systemic arterial pressure. Pulmonary venous obstruction was difficult to measure, but was probably present to some degree in most cases. The gradient between pulmonary vein and right atrium gradient averaged 11 mmHg in 17 patients in whom it was measured (Table 2).

Seven infants had intracardiac, 24 supracardiac type (4 with drainage into the right superior vena cava), and 6 had infracardiac total anomalous pulmonary venous drainage; there were 2 infants with mixed drainage. The most common types encountered are illustrated in Fig. 1.

Surgical techniques

A two-stage correction for total anomalous pulmonary venous drainage has been tried with limited success (Mustard *et al.*, 1962; Behrendt *et al.*, 1972). At present, complete repair at a single operation is


Infracardiac

Supracardiac (Innominate Vein)

Intracardiac (Coronary Sinus)

Supracardiac (Superior Vena Cava)

Fig. 1 *Types of total anomalous pulmonary venous drainage in 39 infants, 1971 to 1975.*

generally preferred. Correction can be carried out either on cardiopulmonary bypass or using deep hypothermia with circulatory arrest. Results reported so far in various series do not clearly indicate superiority of either technique, but most surgeons prefer the latter in small infants. We began to use circulatory arrest with deep hypothermia in 1971 and now use this technique for infants under the age of 6 months.

When preparations for total correction have been completed, babies are taken to theatre where, under general endotracheal anaesthesia, arterial, venous, and urinary catheters are inserted if this has not already been done. Surface cooling to 27° to 28°C nasopharyngeal temperature is accomplished and a midline sternotomy incision is then performed. The ascending aorta is cannulated with a thin walled metal cannula and a single plastic cannula is placed through the right atrial appendage. The ductus arteriosus is ligated if patent and cardiopulmonary bypass is instituted with further cooling to 19°C nasopharyngeal temperature. The aorta is cross-clamped and the patient is exsanguinated into the oxygenator. The superior and inferior venae cavae are occluded and the repair is carried out. The technical details of the repair vary with the type of anomalous drainage.

INTRACARDIAC TYPE OF TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

When the pulmonary veins drain into the right atrium, either directly or by way of the coronary sinus, a good surgical result can be achieved with a relatively simple repair. When the drainage is into the coronary sinus, the coronary sinus is opened back into the left atrium through the patent foramen ovale (Fig. 2). A patch of pericardium or 'dacron' is then placed over the resulting defect to direct the flow into the left atrium. Anteriorly, the patch is sutured into the floor of the coronary sinus thus avoiding the tail of the atrioventricular node (Fig. 3).

SUPRACARDIAC TYPE OF TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

When the pulmonary veins drain through a left-sided vertical vein into the innominate vein, the first step in the repair is the ligation of the ascending vein. The dissection of this vein is carried out outside the pericardium and care is taken to avoid the phrenic nerve and to ligate well above the entry of the left upper pulmonary vein. When circulatory arrest is used, the anomalous vein should not be ligated until the circulation is stopped. When conventional bypass is used, the common pulmonary vein should be incised immediately after ligation of the ascending vein. Observance of these rules will prevent severe pulmonary congestion which occurs if the anomalous vein is ligated too early in the procedure.

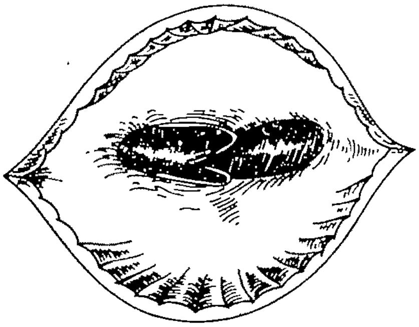


Fig. 2 *Operative technique for total anomalous pulmonary venous drainage to the coronary sinus. The coronary sinus is cut back into the left atrium and the septum between the coronary sinus and foramen ovale excised. PFO, patent foramen ovale; CS, coronary sinus.*

We now prefer the right-sided transatrial approach for the repair of this type of total anomalous pulmonary venous drainage (Shumaker and King, 1961; Gersony *et al.*, 1971). An incision is made transversely in the right atrium, continuing posteriorly through the patent foramen ovale, across the interatrial septum, and horizontally across the posterior wall of the left atrium. Care should be taken to make this incision parallel to and adjacent to the pulmonary vein. The horizontal collecting vein is incised on its anterior surface and an anastomosis is constructed between the posterior left

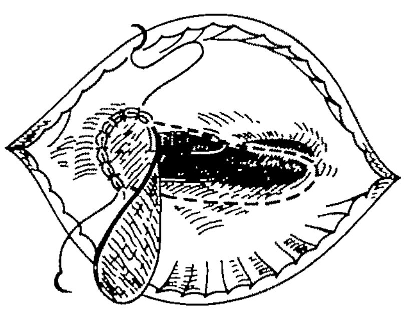


Fig. 3 *A patch is used to redirect pulmonary venous blood to the left atrium. Anteriorly, the suture is placed through the floor of the coronary sinus to avoid its anterior rim. Abbreviations as in Fig. 2.*

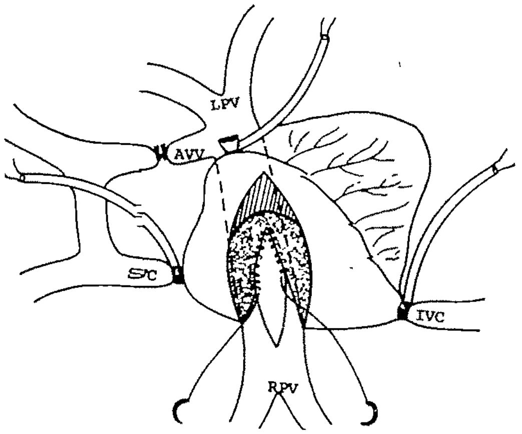


Fig. 4 *Operative technique used for supracardiac total anomalous pulmonary venous drainage. SVC and IVC are occluded, venous cannula removed and ascending vein ligated. Right atrium is then opened across the septum into the left atrium. Horizontal collecting vein is incised and anastomosis to left atrium constructed. LPV, left pulmonary veins; RPV, right pulmonary veins; SVC, superior vena cava; IVC, inferior vena cava; AVV, ascending vertical vein.*

atrium and the common vein (Fig. 4). To ensure an adequate opening, the anastomosis can be carried across the posterior interatrial septum, using a portion of the posterior wall of the right atrium to complete the connection. The cavity of the left atrium can then be enlarged either by shifting the interatrial septum to the right or by enlarging the atrial septal defect and closing it with a generous patch (Fig. 5). This technique has the distinct advantage of allowing the anastomosis to be constructed with the heart and the common pulmonary vein lying in their natural position, thus avoiding kinking or traction at the anastomosis.

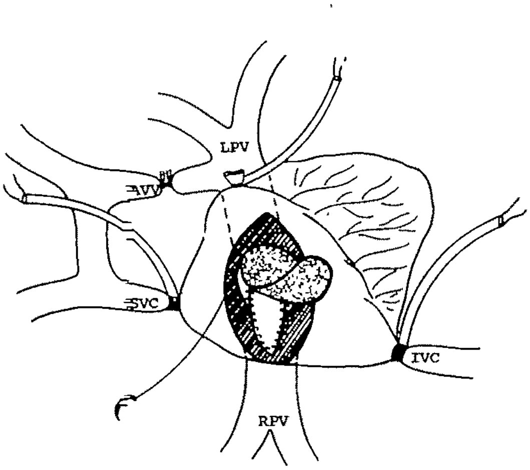


Fig. 5 *Anastomosis is completed. The cavity of the left atrium is being enlarged by closing the atrial septal defect with a patch. Abbreviations as in Fig. 4.*

In a variant of supracardiac total anomalous pulmonary venous drainage, drainage is via an anomalous ascending vein on the right side which enters the back of the right superior vena cava at the level of the confluence of the innominate veins. In all 4 patients with this anatomical variant, the vein was varicose and very friable; extreme care in dissection is therefore advisable.

Construction of the anastomosis with this variant can also be difficult since the horizontal collecting vein is usually high and to the right, causing difficulty in approximating it to the posterior wall of the left atrium.

INFRACARDIAC TYPE OF TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

In the repair of infracardiac type of total anomalous pulmonary venous drainage, we prefer the retrocardiac approach (Fig. 6 and 7). This allows better exposure of the common vein which is orientated vertically. The first step is again ligation of the anomalous vein immediately before beginning the repair. If there is a long distance between the con-

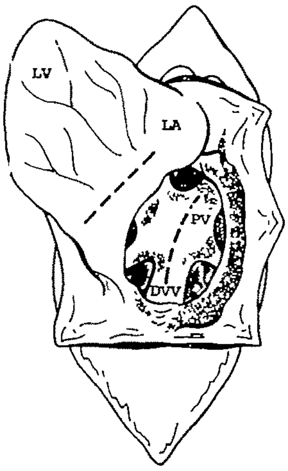


Fig. 6 *Operative technique for infracardiac type. Heart is lifted upwards, pulmonary veins and descending vertical vein are dissected. The incision runs from the left upper pulmonary vein obliquely into the vertical vein. Corresponding incision is made in the left atrium. LV, left ventricle; LA, left atrium; DVV, descending vertical vein; PV, pulmonary vein.*

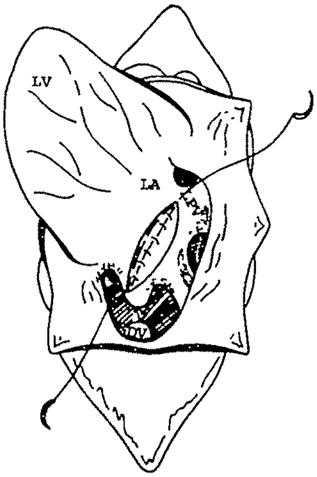


Fig. 7 *The vertical vein is ligated and divided. Anastomosis is performed with continuous suture. LA, left atrium; LV, left ventricle; DV, descending vein; LPV, left pulmonary vein.*

fluence of the pulmonary veins and the left atrium, the descending vertical vein can be doubly ligated and divided, thus allowing the site of the anastomosis to come into closer apposition to the left atrium (Stark *et al.*, 1977). Oblique parallel incisions are then made in the confluence of pulmonary veins and in the posterior wall of the left atrium (Fig. 6). The incision in the common pulmonary vein can be carried down into the upper portion of the dilated ascending vein, allowing a larger anastomosis to be constructed (Fig. 7). The atrial septal defect or patent foramen ovale is then closed through a separate right atriotomy.

MIXED TYPES OF TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

Anomalous drainage does not always follow the same pathways from both lungs or from all lobes. Almost any combination of the standard types of drainage can exist in one patient. Operative techniques must be individualised in this small group of patients, but in general, when an anomalous connection, different from the main drainage, involves only one lobe, it can be left uncorrected without great physiological consequences. In the most common mixed type the left upper lobe vein drains directly into a vertical vein entering the left innominate vein, and there is infracardiac or intracardiac drainage of the remaining pulmonary veins.

Table 3 *Results of operation related to anatomical type of total anomalous pulmonary venous drainage*

Type	*No.*	*Died*
Innominate vein	20	7 (35%)
Coronary sinus or right atrium	7	1 (14%)
Infradiaphragmatic	6	3 (50%)
Right superior vena cava	4	3 (75%)
Mixed	2	0 (0%)
Total	39	14 (36%)

POSTOPERATIVE CARE

Intensive postoperative management of infants with total anomalous pulmonary venous drainage is crucial for survival. Sophisticated monitoring techniques referred to earlier, ventilatory support, and constant attendance by competent personnel are essential. Prevention and treatment of fluid overload and its complications is vital in the management of these infants. Lungs of infants who have had pulmonary oedema are particularly prone to accumulation of interstitial water. Avoidance of volume overload and maintenance of optimal cardiac output are necessary to prevent recurrent pulmonary oedema.

Atelectasis often occurs as a complication in the postoperative period. Ventilatory support either with intermittent positive pressure breathing or continuous positive airway pressure may be needed for a few days. Intensive physiotherapy, starting immediately after operation, is continued throughout the postoperative period. If the proper operation has been performed and these principles are followed, reasonable results can be expected.

Results

Of 39 infants, 14 died in hospital giving an overall mortality rate of 36 per cent. There have been no late deaths. The factor with the most striking effect on mortality was the anatomical type of total anomalous pulmonary venous drainage (Table 3). The mean age, body weight, and degree of pulmonary hypertension present in survivors was roughly equal to that of non-survivors (Table 4).

Table 4 *Comparison of 25 survivors and 14 non-survivors.*

	Survivors	*Non-survivors*
Mean age at operation (d)	89	80
Mean body weight at operation (kg)	4·1	3·8
Mean pulmonary/systemic systolic pressure ratio	0·95	1·00

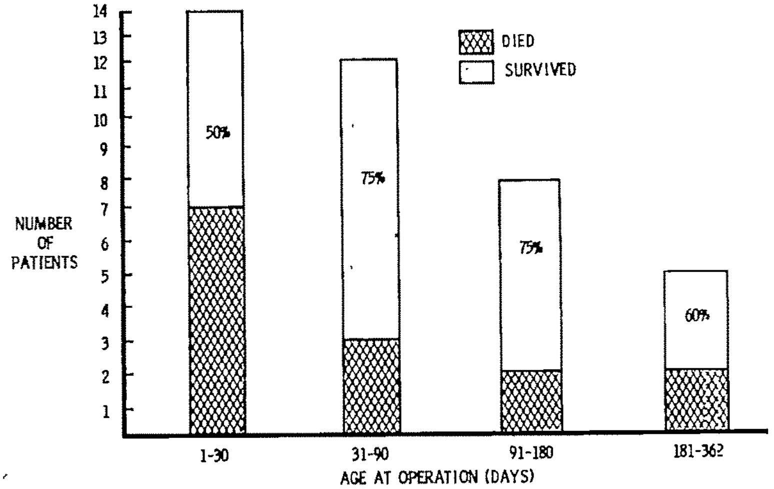


Fig. 8 *Survival rate related to age at operation.*

Survival related to age at operation and to pulmonary/systemic systolic pressure ratio at cardiac catheterisation is illustrated in Fig. 8 and 9.

Pulmonary Histology was examined in all but two of the infants who died, and particular attention was paid to the pulmonary vascular changes. Seven of the 12 showed the arterial changes of grade 2 pulmonary vascular disease, by Heath and Edwards' classification (958). One showed grade 1 changes, while in the remaining 4, who were less than 1 month old, fetal arterial appearances persisted. Similar arterial changes were seen in the different lobes of each case.

The venous changes consisted of endothelial hyperplasia in 9 cases; 2 of these also showed medial hypertrophy. The venous changes tended to be uniform throughout all lobes in 5, but were more severe in the lower lobes than upper lobes in 3; in 1 patient, the changes were restricted to the left lung. Some lymphatic dilatation was seen in 7 of the 12. None had bronchial venous dilatation. There was no constant correlation between the severity of arterial changes and the venous or lymphatic changes.

Discussion

Lemoine, Gersony, and Applebaum and their colleagues have also observed recent improvements in results of surgical correction of total anomalous

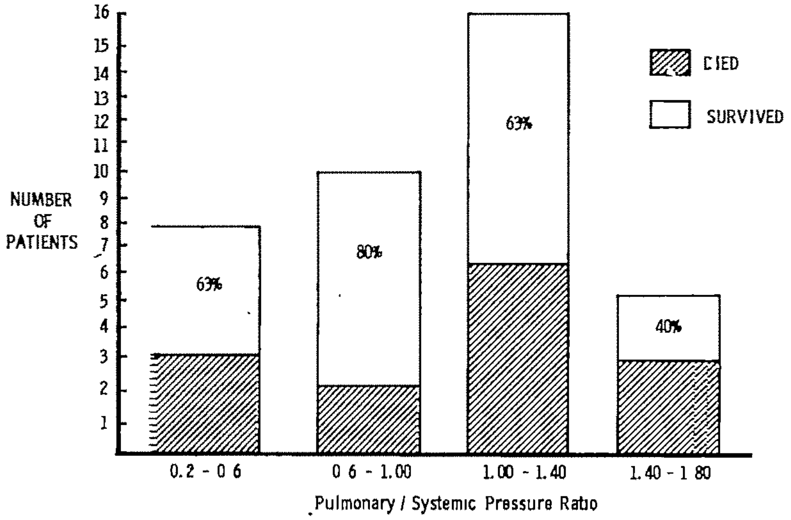


Fig. 9 *Survival rate related to preoperative pulmonary/systemic systolic pressure ratio.*

Table 5 *Results of operation for total anomalous pulmonary venous drainage in infants in four large series*

Author	*No.*	*Died No.*	%
Appelbaum *et al.* (1975) 1968–1974	31	15	48
Lemoine (1975) 1967–1974	45	15	33
Gersony *et al* (1975, personal communication) 1969–1975	29	14	48
This study (1976) 1971–1975	39	14	36
Total	144	58	40

pulmonary venous drainage in infancy (Table 5) (Lemoine, 1975; Gersony *et al.*, 1975, personal communication; Applebaum *et al.*, 1975). The most significant improvement has been the increased survival of the younger infants. Before 1971, no infant less than 3 months of age had survived operation for total anomalous pulmonary venous drainage in this unit. In the current series, 16 of 26 (62%) survived. The success rate is still slightly lower in the group less than 1 month of age (Fig. 8). This could be related to the fact that the more severe lesions are the ones that present shortly after birth; it is significant that the infants in this series with the infracardiac type of total anomalous pulmonary venous drainage had a mean age of 3 weeks at operation, compared with the mean age of 12 weeks for the whole group.

The degree of pulmonary hypertension before operation had very little effect on ultimate survival. The mean value of the pulmonary/systemic systolic pressure ratio was similar in the survivors and non-survivors (Table 4). Further scrutiny of this relation shows slightly decreased survival in the 5 patients with pulmonary/systemic systolic pressure ratios greater than 1·4. This difference is not statistically significant (Fig. 9). In the relative lack of correlation between the degree of pulmonary hypertension and survival, our experience contrasts with that from other centres and indeed with our own past experience (Wukasch *et al.*, 1975; Behrendt *et al.*, 1972).

Mortality is most closely related to the anatomical type of total anomalous pulmonary venous drainage (Table 3). The coronary sinus or right atrial type had the lowest operative mortality. Only 1 of the 7 infants died; this patient failed to come off bypass and at necropsy was found to have a severely hypoplastic left ventricle. A high survival rate with this type has also been observed by others. All 15 patients in Lemoine's series (1975) and all 7 patients in Gersony *et al.*'s (1975) survived operation. Pulmonary venous obstruction is uncommon in this type and the repair is technically easy.

The mortality rate for the supracardiac type, which accounted for over 50 per cent of the patients in our series, was similar to the mortality for the overall group (Table 3). Four of our patients had drainage to the right superior vena cava, and 3 of these died. The reason for this high mortality is not entirely clear. Bleeding from the very friable ascending vein and difficulties in approximating the common pulmonary vein to the posterior wall of the left atrium may be important factors.

The infracardiac type was associated with a 50 per cent mortality (Table 3). All in this group had obstructed pulmonary venous drainage and were very ill at the time of admission and operation.

When the causes of death in 14 patients were examined, pulmonary oedema was found in 12. Arrhythmias were responsible in 2 patients, fluid overload in 1, and stenosis of the anastomosis in 1. The common vein, left atrium, or left ventricle was hypoplastic in 4, and no cause was found for persistent fatal pulmonary congestion in 4 cases. It was possible that the anastomosis was kinked, or that an adequate sized left atrial reservoir had not been constructed (Parr *et al.*, 1974); precise assessment of these factors is very difficult at necropsy.

There are obviously problems with the management of total anomalous pulmonary venous drainage in infancy which remain unsolved, but the substantial recent increase in survival rate is encouraging. We attribute the improved results to: (1) early recognition and prompt referral, (2) an aggressive approach to diagnosis involving complete cardiac catheterisation and angiocardiography to show the exact site of drainage of all pulmonary veins and to exclude any additional cardiac lesions, (3) vigorous preoperative care, (4) early complete correction including construction of a large anastomosis and enlargement of the left atrium when indicated, and (5) intensive postoperative management, paying particular attention to fluid balance and treatment of pulmonary complications.

We thank the Henry Ford Hospital and Appleton-Century-Crofts for the use of Fig. 2, 3, 4, 5, 6, and 7 from the article 'Surgical treatment of total anomalous pulmonary venous drainage in infants' by J. Stark, D. Clarke, M. de Leval, and J. F. N. Taylor, to be published in the Proceedings of 2nd Henry Ford International Symposium on Cardiac Surgery, held in Detroit, U.S.A., in October 1975.

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British Heart Journal, 1977, **39**, 445–450

Incidence of congenital heart disease in Blackpool 1957-1971

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In the 15 years from 1957 to 1971, there were 57 979 births in a circumscribed population in North-West England. The requirements for a valid survey of the incidence of congenital heart disease were largely met. The necropsy rate for all stillbirths and neonatal deaths in the population was 93 per cent. Diagnosis of the type of heart lesion was by necropsy in 50 per cent, cardiac catheterisation in 19 per cent, operation in 5 per cent, and clinical observations only in 26 per cent. The incidence of congenital heart disease was 6·8 per 1000 total births and 5·9 per 1000 live births. The overall incidence has remained unchanged over the 15 years, but there were trends suggesting an increase in the incidence of uncomplicated ventricular septal defect and of endocardial cushion defect and a decrease in the incidence of ventricular septal defect with right ventricular outflow obstruction and of hypoplastic left heart. We have observed seasonal variations in total incidence and in incidence of some common individual lesions.

This paper reports the incidence of congenital heart disease in 57 979 births over 15 years in a combined urban and rural area of North-West England. This information is needed to provide basic data for studies of aetiological factors and to plan the facilities required for the management of affected children.

The incidence of congenital heart disease is difficult to ascertain accurately, mainly because it is unrecognisable at birth in an appreciable proportion of cases. The requirements for a successful survey may be stated as follows:

(1) A well-defined population for study.
(2) This population should be as large as possible provided that cases and suspected cases can be seen personally to obtain consistency in diagnosis.
(3) There must be comprehensive routine examinations of neonates, infants, and school entrants.
(4) Cases should not be sent directly out of the district for diagnosis so that they are not recorded.
(5) Few cases should leave the district before recognition.
(6) A high necropsy rate is essential especially for stillborn babies and those dying in the first week who may have no signs suggesting heart disease.

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Subjects and methods

The Blackpool district is well demarcated, being bounded on three sides by water barriers, while the fourth landward boundary is in sparsely populated country. The population, which has increased from about 250 000 to 300 000 is served by one district hospital (Victoria). This hospital has departments of cardiology and cardiac surgery, being a subregional centre for these specialities. The number of live births, stillbirths, and neonatal deaths occurring in the district was notified to us by the Medical Officers of Health.

The distribution of births by place of delivery is shown in Table 1. All babies were examined after birth and before discharge by the paediatric staff in the consultant obstetric unit. General practitioners carried out the routine examination of babies born in their units and at home. One of us (J.P.B.) visited the general prac-

Table 1 *Distribution of births by place of delivery*

Period	*Consultant obstetric units*	*General practitioner hospitals*	*Home*	*Total numbers*
1957–1961	49%	28%	23%	18 073
1962–1966	54%	24%	22%	20 794
1967–1971	63%	24%	13%	19 112
Total numbers	32 091	14 542	11 346	57 979

Table 2 *Method of diagnosis according to mutually exclusive list for common lesions*

Lesion	*Method of diagnosis*				*Total cases*
	Necropsy	*Cardiac catheterisation*	*Operation*	*Clinical*	
Ventricular septal defect uncomplicated	24%	23%	—	53%	110
Ostium secundum atrial septal defect	68%	27%	—	5%	41
Ventricular septal defect with right ventricular outflow obstruction	69%	22%	—	9%	32
Endocardial cushion defect	69%	14%	—	17%	29
Coarctation of aorta	68%	4%	20%	8%	25
Persistent ductus arteriosus uncomplicated	5%	27%	59%	9%	22
Transposition of great arteries	85%	15%	—	—	20
Aortic stenosis	21%	43%	—	36%	14
Pulmonary stenosis isolated	11%	45%	22%	22%	9
All cases	50%	19%	5%	26%	395
Liveborn cases	41%	22%	6%	31%	338

titioner hospitals weekly to examine babies with suspected abnormalities and to encourage good standards of care. Babies with symptoms were visited at once or sent by their doctors to Victoria Hospital. Suspected cases of congenital heart disease, discovered subsequently when the children were ill or at routine clinic or school examinations, were seen at Victoria Hospital. Cases entering the district after birth were noted, but not included in the series.

Necropsies were carried out on 93 per cent of babies stillborn or dying in the neonatal period wherever they were born. The majority of infants and older children dying in Victoria Hospital also had a necropsy and reports were received on all examinations carried out for H.M. Coroner. One at least of the authors usually attended the necropsies or examined the specimens later.

To decide which cases to include we adopted the definition of congenital heart disease used by Mitchell *et al* (1971): 'A gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance'. Lesions have been classified according to the scheme of the International Society of Cardiology (1970). Infants with systolic murmurs in whom a definite clinical diagnosis, such as ventricular septal defect, could not be made clinically have not been included. When these murmurs disappeared over a few weeks to years they were classified as transient systolic murmurs. No children with systolic murmurs considered innocent have been included.

Results

RECOGNITION

Seventy-four per cent of the cases of congenital heart disease were recognised by the age of 3 months, 82 per cent by one year, and 90 per cent by

Table 3 *Incidence of common lesions*

Lesion	*ISC code*	*Live births*		*Total births*	
		No.	*Incidence per 10 000 births*	*No.*	*Incidence per 10 000 births*
Ventricular septal defect uncomplicated	770	95	16·5	110	19·0
Ostium secundum atrial septal defect	110	28	5·0	41	7·0
Ventricular septal defect with right ventricular outflow obstruction	780	29	5·0	32	5·5
Endocardial cushion defect	200	25	4·5	29	5·0
Coarctation of aorta	020	19	3·5	25	4·5
Persistent ductus uncomplicated	174	22	4·0	22	4·0
Transposition of great arteries	602	19	3·5	20	3·5
Aortic stenosis	070	14	2·5	14	2·5
Hypoplastic left heart	260	11	2·0	13	2·0
Single ventricle	520	5	1·0	10	1·5
Pulmonary stenosis isolated	446	9	1·5	9	1·5
Truncus arteriosus	740	4	0·5	8	1·5
Total anomalous pulmonary venous return	470	7	1·0	7	1·0
Tricuspid atresia	701	5	1·0	5	1·0
Miscellaneous	—	46	8·0	50	8·5
Total		338	59·5	395	68·0

ISC = International Society of Cardiology

3 years. Among common individual lesions late recognition occurred predominantly in persistent ductus (73% by three years) and aortic stenosis (64% by three years).

DIAGNOSIS

In 74 per cent of cases diagnosis was based on the results of catheterisation or findings at operation or necropsy. Table 2 shows the method of diagnosis for some common lesions according to a mutually exclusive list in the order—necropsy, cardiac catheterisation, operation, or clinical only.

OVERALL INCIDENCE

In the years 1957 to 1971 there were 57 979 births in the district, with 395 cases of congenital heart disease giving an incidence of 6·8 per 1000 total births. When stillbirths were excluded there were 56 982 births with 338 cases of heart anomalies, an incidence of 5·9 per 1000 live births. The number of undiagnosed cases born in 1957 to 1971 but entering the district after birth was 18. These were not included in the series.

INCIDENCE OF INDIVIDUAL LESIONS

The incidence of the common lesions on a population basis for both live births and total births is shown in Table 3. The incidence of transient systolic murmurs was 0·5 per 1000 live births.

CHANGES IN INCIDENCE

To discover if there has been any major change in incidence, we have divided the 15-year period of study into three 5-year periods. To make the three periods comparable, only cases identified within 5 years of birth have been included, in order not to underestimate incidences in the last period.

The overall incidence of congenital heart disease has been remarkably constant (Table 4). Some individual lesions have shown changes. Three lesions have steadily declined in incidence, while two have increased (Table 5). The only significant change was the increase in frequency of uncomplicated ventricular septal defect ($\chi^2=7{\cdot}608$; $P<0{\cdot}05$).

Table 4 *Incidence of congenital heart disease recognised within 5 years of birth*

Period	*Total births*	*Congenital heart disease* *No.*	 *Incidence/1000 births*
1957–1961	18 073	113	6·3
1962–1966	20 794	136	6·5
1967–1971	19 112	124	6·5
1957–1971	57 979	373	6·4

SEASONAL VARIATIONS

These have been considered in relation to time of conception rather than birth. To obtain larger numbers for this analysis we have included cases born in 1972 and 1973. Figures for seasonal variations in birth rate in the district by month of last menstrual period were not available. We have therefore had to use as a control group those babies stillborn or dying in the neonatal period from acquired disease. Our studies have shown that these do not have a seasonal incidence.

The noteworthy findings in our figures are shown in Table 6. A greater risk of developing congenital heart disease is shown for conceptions in summer though the figures do not reach statistical significance. Six of the 12 commonest lesions showed this tendency though the figures are significant only for persistent ductus arteriosus and aortic stenosis.

Table 5 *Lesions showing change of incidence during the 15-year period*

Lesion	*1957–1961*	*1962–1966*	*1967–1971*
Ventricular septal defect with right ventricular outflow obstruction	15 (8·3)	10 (4·8)	7 (3·7)
Hypoplastic left heart	7 (3·9)	5 (2·4)	1 (0·5)
Ostium secundum atrial septal defect	16 (8·9)	13 (6·3)	10 (5·2)
Ventricular septal defect uncomplicated	20 (11·1)	43 (20·7)	43 (22·5)
Endocardial cushion defect			
All cases	5 (2·8)	16 (7·7)	8 (4·2)
Cases with Downs syndrome	1 (0·6)	8 (3·8)	7 (3·7)

Incidence per 10 000 births in parentheses.

Table 6 *Half-yearly seasonal incidence by month of last menstrual period*

Lesion	*April–September*	*October–March*
All cases	237 (54·9%)	195 (45·1%)
Ventricular septal defect uncomplicated	70 (57%)	53 (43%)
Ostium secundum atrial septal defect	24 (62%)	15 (38%)
Endocardial cushion defect	19 (61%)	12 (39%)
Persistent ductus arteriosus	18 (75%)	6* (25%)
Aortic stenosis	12 (80%)	3* (20%)
Pulmonary stenosis isolated	8 (67%)	4 (33%)
Transposition of great arteries	7 (30%)	16* (70%)

*$P<0{\cdot}05$.

Note: In 1957 to 1969 the last menstrual period was in April to September in 50·2 per cent of 1004 babies stillborn or dying in neonatal period from acquired disease.

One lesion, transposition of the great arteries, showed the opposite trend with significantly more conceptions in winter.

Discussion

The first essentials in any study of congenital heart disease are to define the term and to state clearly the classification that has been used. It is also important to show the proportion of cases diagnosed by conclusive techniques. These precepts have been followed in our survey but not in some others. The other major consideration is the proportion of cases actually identified.

A well-defined population has been studied, making the collection of statistics reliable. Blackpool is 50 miles from a city centre, and Victoria Hospital has departments of cardiology and cardiac surgery; therefore, we have no reason to believe that any children found to have possible heart lesions are not referred to us in the first instance. From one-half to two-thirds of all babies born in the district were screened by the staff of the paediatric unit. General practitioners and clinic doctors, who carried out other routine examinations, were encouraged to refer cases if there was any suspicion of an abnormality. A high necropsy rate has been maintained throughout the 15 years so that very few heart lesions can have been missed in children with fatal illnesses.

A possible source of error in any survey is undiagnosed cases leaving the district. These are thought to be few for two reasons. First, we have shown that the majority of cases are recognised early in life. Secondly, the number of undiagnosed cases entering the district who were born in 1957 to 1971 is small. If it is assumed that approximately the same number have left the district unrecognised, then our incidence of congenital heart disease is an underestimate by only 0·3 per 1000 births. For these reasons we believe that the detection of cases has been as complete as is likely to be achieved in practice.

INCIDENCE

The overall incidence of detected congenital heart disease was 6·8 per 1000 total births. Remembering our estimate of undiagnosed cases leaving the district, it seems reasonable to state that the incidence is just over 7 per 1000 total births. This is in accord with the findings of the few modern surveys of this type. In particular, the incidence is similar to that found in Liverpool in 1960 to 1969 (Kenna *et al.*, 1975). Thus, it seems that the incidence in urban and rural areas is similar to that in the big cities.

When stillbirths were excluded the incidence dropped by approximately 1 per 1000 births. The figure of 5·9 per 1000 livebirths agrees closely with the 5·7 per 1000 livebirths found by Feldt *et al.* (1971) in Olmsted County, Minnesota, in 1950 to 1969. Again, allowing for the loss of undiagnosed cases the incidence in livebirths in the Blackpool district may be taken as just over 6 per 1000. It seems reasonable to use this figure when estimating the facilities required for the medical care of these children.

INCIDENCE OF INDIVIDUAL LESIONS

Comparison of the Blackpool series with the multicentre study in the USA (Mitchell *et al.*, 1971) showed no significant differences in the incidence of common lesions, except for isolated pulmonary stenosis, which was much less frequent in Blackpool (Table 7).

When our figures were compared with those from Liverpool (Kenna *et al.*, 1975) four significant differences were shown. There was a lower incidence of pulmonary stenosis and persistent ductus arteriosus in our series and a higher incidence of atrial septal defect and Fallot's tetralogy. This comparison highlights the need for all workers to use an agreed classification of heart lesions. In Table 3 our numbers for ventricular septal defect with right ventricular outflow obstruction include cases with pulmonary atresia as in the ISC classification, but in Table 7 we have included only those cases with pulmonary stenosis to compare with the Liverpool figure for 'Fallot's tetralogy'. Further, we have assumed that 'atrial septal defect'

Table 7 *Incidence of common lesions in three series*

Lesion	*Blackpool 1957–71*	*Liverpool 1960–69*	*Multi-centre U.S.A.*
Ventricular septal defect uncomplicated	110 (19·0)	261 (16·0)	133 (23·5)
Atrial septal defect uncomplicated	54* (9·5)	54 (3·5)	40 (7·0)
Fallot's tetralogy	26* (4·5)	42 (2·5)	27 (5·0)
Coarctation of aorta	25 (4·5)	54 (3·5)	30 (5·5)
Persistent ductus arteriosus	22* (4·0)	106 (6·5)	35 (6·0)
Transposition of great arteries	20 (3·5)	59 (3·5)	11 (2·0)
Aortic stenosis	14 (2·5)	52 (3·0)	16 (3·0)
Pulmonary stenosis isolated	9** (1·5)	83 (5·0)	37 (6·5)
Total births	57 979	163 692	56 109

Incidence/10 000 births in parentheses.
*Significant difference between Blackpool and Liverpool (χ^2 test; $P < 0·05$).
**Significant difference between Blackpool and both Liverpool and U.S.A.

in the Liverpool series includes ostium secundum and primum defects, but not common atrioventricular canal which is listed separately. Our figure for comparison, therefore, combines ostium secundum and primum defects, but the number of atrial septal defects is significantly higher than in the Liverpool series even if only ostium secundum defects are included. It seems that differences in classification do not explain the different incidence of certain lesions in near neighbours Blackpool and Liverpool. Missed cases cannot be completely ruled out, but this seems an unlikely explanation for the difference in the incidence of the readily recognised Fallot's tetralogy, for example.

The low incidence of isolated pulmonary stenosis compared with both the American and Liverpool series was a feature. We have used strict diagnostic criteria for this lesion (a gradient greater than 25 mmHg at catheterisation), and it is possible that some cases we have classified as idiopathic dilatation of the pulmonary artery would have been included as mild pulmonary stenosis by other workers. However, even if our figures for the two lesions are combined, the incidence is still significantly lower than in the other two series.

In our series exclusion of stillbirths did not affect the incidence of most lesions. Those showing a lower incidence were those more frequently associated with other severe malformations, except in the case of coarctation. However, postductal coarctation might be expected to cause heart failure *in utero* in some cases.

There could be advantages in treating those children whose lesions required advanced surgery, in a very few centres in this country. If this became accepted policy, information now available about the incidence of individual lesions would be valuable in assessing workloads, though possible variations between different areas would have to be considered.

CHANGES IN INCIDENCE

Two lesions, ventricular septal defect with right ventricular outflow obstruction and hypoplastic left heart, declined in incidence during the period of study. It is certain that detection of cases with these lesions is complete and, though the differences did not reach statistical significance, the fall was steady in each case and should not be ignored. There was also a suggestion of a decline in the incidence of ostium secundum atrial septal defect.

Two lesions, uncomplicated ventricular septal defect and endocardial cushion defect, have increased in incidence. The greater number of ventricular septal defects is significant; this increase includes proven cases, but more of those diagnosed only clinically. Possibly more cases in which the defect closed spontaneously were recognised as the study progressed, a view supported by an increased number of transient systolic murmurs. However, if improved diagnosis were a major factor this would have been expected to increase the overall incidence of heart disease, which was not observed. A decrease in frequency of some lesions may have masked the effects of improved diagnosis, but this seems unlikely to have occurred so exactly. On balance, there appears to have been a real increase in the incidence of uncomplicated ventricular septal defect.

The increase in endocardial cushion defect was partly the result of its association with Down's syndrome. This condition was nearly twice as frequent in the second period as in the first and third periods. In the last period more cases of Down's syndrome had endocardial cushion defects.

It is to be hoped that variations in the incidence of lesions, with time, or between different areas, may provide pointers to the aetiological factors involved. Lastly, it should be emphasised that while there may be changes in the number of operations needed for specific lesions, the percentage of children requiring diagnosis, follow-up, and treatment has not declined.

SEASONAL VARIATIONS

Kenna *et al.* (1975) suggested that a seasonal variation should be seen in at least three separate studies to be acceptable and we agree with this. Our finding that more cases of congenital heart disease were conceived in April to September is in accord with that of Feldt *et al.* (1971). They showed births of babies with heart disease to be highest in winter (December to February) decreasing through spring and summer, while in our series conceptions were high in April to June, decreased during the next two quarters, and began to increase a little in January to March. Campbell (1965) reported a seasonal incidence for births of children with persistent ductus but the peak was from August to November, contrasting with our findings of a summer peak for conceptions. Our finding of more conceptions in summer for aortic stenosis and in winter for transposition of the great arteries do not appear to have been reported previously, but it must be remembered that the numbers were small. No consistent pattern has so far emerged for individual lesions but, clearly, workers should continue to report any seasonal variations in the birth of children with congenital heart disease. Our own studies are continuing.

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Two unusual cases of intra-atrial gap

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Two cases are described in which, during investigation of rhythm disturbances, it was shown that, by delivering atrial stimuli of increasing prematurity, a point was reached where the artificial stimulus failed to induce an atrial response. However, with even more premature stimulations, atrial responses were again observed. These observations are best explained by a gap phenomenon in which very early stimuli delivered during the effective refractory period of the atria were delayed long enough in the exit area around the pacing electrode to allow atrial recovery.

The phenomenon of 'gap' in atrioventricular conduction was first described by Moe *et al.* (1965). During experiments on dogs, they observed a zone in the cardiac cycle when atrial premature beats were not transmitted to the ventricles whereas atrial beats of greater or lesser prematurity were normally conducted to the ventricles. The atrioventricular gap phenomenon occurs when the effective refractory period of a distal site (for example, the His-Purkinje system) is longer than the functional refractory period of a proximal site (for example the AV node), and when closely coupled stimuli are delayed long enough at the proximal site to allow recovery at the distal end (Wu *et al.*, 1974).

At present, at least 6 types of gap phenomenon in atrioventricular conduction have been recognised; they differ from one another in the sites of proximal delay and distal block (Damato *et al.*, 1976).

In this paper, we report on two patients in whom the electrophysiological findings strongly suggested an unusual gap phenomenon where the exit area around a pacing electrode was the site of proximal delay and the atria the distal site with relatively long effective refractory period.

Methods

Electrophysiological investigations were carried out, after informed consent, on 2 patients with rhythm disturbances. The studies were performed in the supine, non-sedated, post-absorptive state. His bundle recordings were obtained by the technique described by Scherlag *et al.* (1969), using a bipolar electrode catheter introduced percutaneously into the femoral vein. Two other bipolar electrode catheters were employed, the first to stimulate the high lateral wall of the right atrium and the second to record the high right atrial electrogram.

The His bundle electrogram, high right atrial electrogram, and 2 surface leads were recorded simultaneously on a 4-channel Elema Mingograf 81 at a paper speed of 100 mm/s. The stimuli were 2 ms square waves approximately equal to twice diastolic threshold and were delivered using a JS-U2 multipurpose programmable stimulator.

During programmed stimulation, the test stimuli were given after each eighth driving stimulus or spontaneous beat, the coupling interval being decreased by decrements of 5 ms.

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Results

CASE 1

The patient was a 56-year-old man who had had an acute anterolateral myocardial infarct in September 1975. He was admitted in January 1976 for treatment of cardiac failure with digitalis and diuretics. Investigations at that time showed a large parietal left ventricular aneurysm, a totally occluded left anterior descending artery with poor distal perfusion, and significantly stenosed left circumflex and right coronary arteries. He had recurrent episodes of ventricular tachycardia for which an electrophysiological study was undertaken about one month later.

During sinus rhythm at 100/min the AH and HV intervals were 130 ms and 40 ms, respectively.

The so-called sinoatrial conduction time was 62·5 ms.

Atrial premature stimuli were introduced at a cycle length of 400 ms (Fig. 1 and 2). As the S1-S2 interval was decreased from 360 to 290 ms, the HRA1–HRA2 decreased similarly. When the S1-S2 interval was further shortened, the HRA1-HRA2 intervals were seen to leave the line of identity, thus indicating increased S2-HRA2 delay. At S1-S2 intervals of 260, 255, 250, and 245 ms, S2 was followed by no atrial response though the driving stimulus (S3) falling immediately after S2, did induce an atrial depolarisation. Surprisingly, the S2 stimuli placed 240 and 235 ms after S1 were followed by atrial contractions, but the S2-HRA2 intervals were prolonged and the two corresponding HRA1-HRA2 intervals were approximately equal to those recorded immediately before the gap.

CASE 2

Case 2 was a 58-year-old woman who had had an asymptomatic bradycardia for several years. In 1975, her electrocardiogram showed a junctional rhythm at 53/min with ventricular ectopic beats. Isoprenaline, administered orally, produced a slight increase in heart rate, but was poorly tolerated. In March 1976, she complained of dyspnoea and was found to be hypertensive (220/100 mmHg). The electrocardiogram still showed sinus bradycardia alternating with junctional rhythm.

The electrophysiological investigation yielded the following results. At rest, at a basic cycle length of 960 ms, the AH and HV intervals were 90 and 45 ms, respectively. The sinoatrial conduction time could not be measured, no plateau zone being found on the curve plotting the return cycles against the test cycles. Atrial pacing at 120/min and 140/min was followed by cardiac pauses longer than 2000 ms. A diagnosis of sinoatrial disease was thus made.

Atrial premature stimuli were introduced at a cycle length of 545 ms (Fig. 3 and 4). The curve obtained by plotting the S1-S2 intervals against the HRA1-HRA2 intervals followed the line of identity

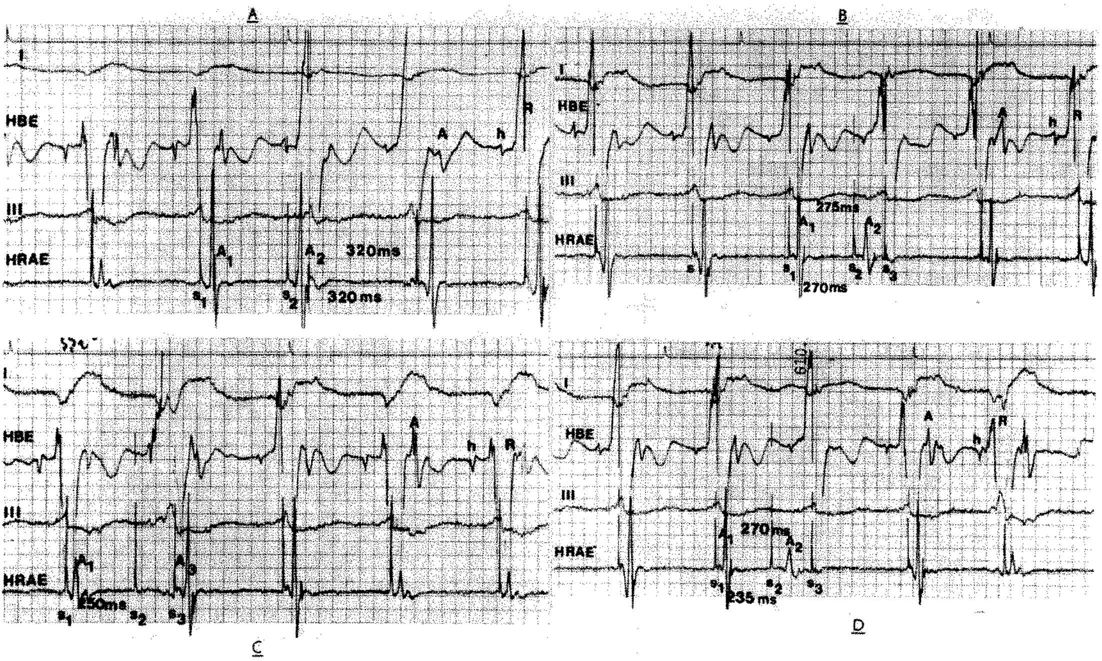

Fig. 1 *Records of leads I and III of the standard electrocardiogram, and of the His bundle (HBE) and high right atrial (HRAE) electrograms. Paper speed 100 mm/s. Basic driving cycle length 400 ms. (A) At an S1-S2 interval of 320 ms, the interval between the atrial responses of the HRAE was also 320 ms. (B) At an S1-S2 of 270 ms, the corresponding A1-A2 interval was slightly longer (275 ms) indicating a small prolongation of the latency time between stimulus artefact and atrial deflection. (C) The stimulus falling at 250 ms evoked no atrial response, though the next stimulus (S3) was conducted. (D) Following S2 placed 235 ms after S1, an atrial response was again observed. (See text for further description.)*

from 420 to 305 ms. For S1-S2 times of 300 ms or shorter, lengthening of the S2-HRA2 delay was seen to shift the curve upward. The S2 stimuli falling 255 and 250 ms after S1 did not evoke atrial responses though the pacing stimulus (S3) falling immediately after S2 induced an atrial depolarisa-

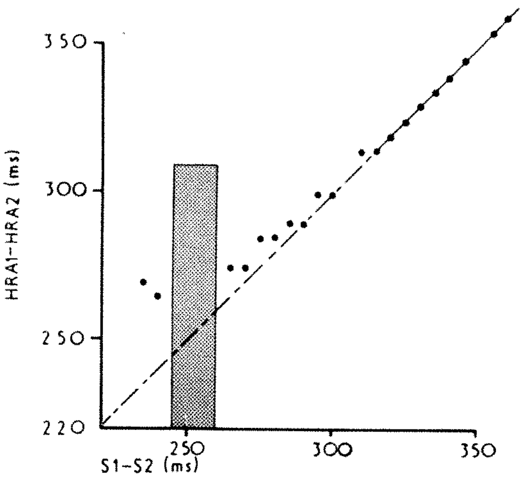

Fig. 2 *Case 1. S1-S2 intervals plotted against HRA1-HRA2 intervals. Basic cycle length 400 ms (150/min). The line of identity was followed for S1-S2 intervals of 360 to 290 ms. A gap in atrial responses was observed at S1-S2 intervals of 260, 250, and 245 ms. Atrial excitation resumed at S1-S2 intervals of 240 and 235 ms. Beyond this point, no further atrial response could be evoked. Note that the last two HRA1-HRA2 intervals were approximately as long as those seen before the gap in atrial responses.*

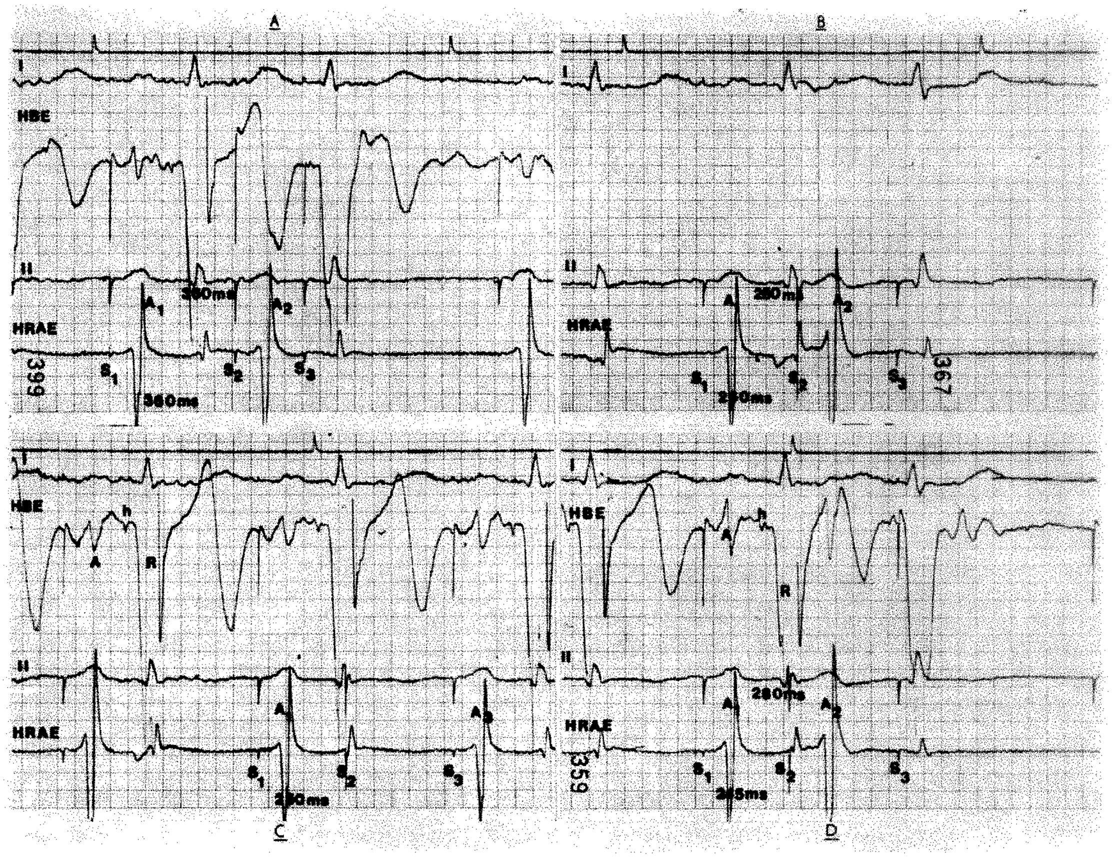

Fig. 3 *Case 2. Leads I and II are shown with the HBE and HRAE. Paper speed is 100 mm/s. The basic driving length is 545 ms. At an S1-S2 interval of 360 ms (A), the distance between the atrial responses of the HRAE was also 360 ms. At an S1-S2 of 260 ms (B), the corresponding A1-A2 interval was 280 ms indicating a prolongation of latency time between stimulus artefact and atrial deflection. The atrial stimulus falling 250 ms after S2 (C) failed to evoke any atrial response but the next extrastimulus succeeded in stimulating the atrial chambers (D).*

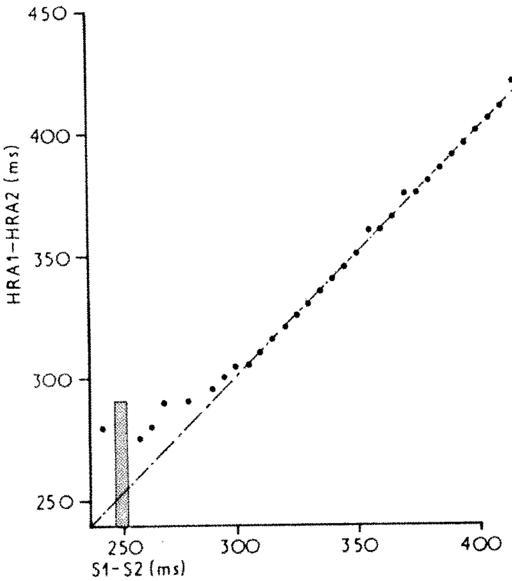

Fig. 4 *Case 2. S1-S2 intervals plotted against HRA1-HRA2 intervals. Basic cycle length 545 ms (110/min). The line of identity was followed from 420 to 305 ms. A gap in atrial responses was observed at S1-S2 intervals of 255 and 250 ms. Atrial excitation reappeared at 245 ms, but with a HRA1-HRA2 interval greater than those seen before the interruption in atrial responses.*

tion. Finally, at an S1-S2 interval of 245 ms, an atrial deflection was again obtained; as in the first case, the S2-HRA2 delay was greatly prolonged in such a way that the HRA1-HRA2 interval was as long as it had been before the gap in atrial responses.

Discussion

These two cases were thought to deserve discussion because of the unusual response to programmed atrial pacing. Premature atrial stimuli were delivered progressively earlier in the cardiac cycle. With increasing prematurity, a zone was reached in which premature atrial responses could no longer be induced. However, if the stimuli were made even more premature, atrial excitation resumed.

There are several possible explanations for this phenomenon. The first to be considered is that small displacements of the catheter tip might be responsible for the fact that some stimuli were not followed by atrial excitation. This explanation is unlikely: in these two cases the phenomenon under discussion occurred only at a critical moment of the cardiac cycle close to the end of the atrial effective refractory period; moreover, the driving stimulus, which directly followed the impulse which was not conducted, did induce a normal atrial response.

Another possible explanation is a phase of supernormal excitability. Though supernormal excitability and conduction has been documented in animal and human experiments, intracellular stimulation methods indicate that not all cardiac cells can exhibit this property (Spear and Moore, 1976). Supernormal excitability has been observed in the His-Purkinje system (Spear and Moore, 1974) and in specialised atrial fibres (Childers, 1974) and in specialised atrial fibres (Childers *et al.*, 1968). It has not been documented in the AV node (Merideth *et al.*, 1968), the bundle of His (Spear and Moore, 1974), or in atrial or ventricular muscle (Childers *et al.*, 1968; Spear and Moore, 1974). In our 2 cases, one cannot rule out the possibility of direct stimulation of specialised atrial fibres by the spacing electrode. In addition to the classical supernormal phase, minimal changes of excitability are known to occur during the relative refractory period. They have been described as 'dips' in the strength-interval curve (Castellanos and Lemberg, 1969) and could account for the behaviour of the atrial responses in our two patients, especially if one considers the fact that the intervals of non-responsiveness were indeed very narrow. Nevertheless, the break in the J-shaped curve obtained by plotting the S1-S2 intervals against the HRA1-HRA2 strongly suggests an unusual form of gap phenomenon.

In reports on intraventricular and atrioventricular conduction, the conduction system has been conceived as a linear structure consisting of multiple components showing differences in their electrophysiological properties. Two conditions were said to be necessary for the development of the gap phenomenon (Wu *et al.*, 1974). These are (a) a distal site with an effective refractory period longer than the functional refractory period of proximal tissues and (b) a proximal site with a functional refractory period which allows enough delay between impulses to ensure that the effective refractory period of the distal site is exceeded.

In our cases, we are not actually dealing with the conduction of an impulse but with a response of the atrial myocardium to an activation stimulus. Though it may appear difficult to relate these atrial activation gap observations to the model used to explain the mechanisms of atrioventricular gap phenomena, one can, in the present situation, describe the atrial musculature as made up of 2 components in series: the exit area around the catheter tip (proximal site) and the rest of the atrial myocardium (distal site).

The exit area from a pacing electrode is known to share some properties with conducting tissues. Exit block around a pacing electrode has been recognised (Preston *et al.*, 1966), and may be manifested as a Wenckebach phenomenon (Peter *et al.*, 1976), or as a gradual prolongation of exit time from a pacemaker potential (Pick, 1973). Increase in latency time between the stimulus artefact and the high right atrial deflection has also been reported, during programmed atrial stimulation, when the coupling intervals are sufficiently short (Wu *et al.*, 1974).

In our cases, as the S1-S2 interval was decreased the HRA1-HRA2 intervals followed the line of identity along its upper portion. With further decrease in S1-S2 interval, the HRA1-HRA2 interval continued to decrease but to a lesser extent, indicating an increase of latency time (S2-HRA2). This feature can be interpreted as showing increasing first degree exit block around the pacing electrode. To account for the reappearance of atrial responses after the interruption of the J-shaped curve, one can reasonably hypothesise that at a critical S1-S2 interval, the proximal delay in the exit area could be sufficiently long for some stimuli apparently falling within the atrial effective refractory period to activate the atria.

If this interpretation is correct the two reported cases would represent unusual examples of an intra-atrial gap which to the best of our knowledge, has not hitherto been described.

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Infective endocarditis caused by *Streptococcus mutans*

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Members of the viridans group of streptococci are the commonest causes of bacterial endocarditis. However, Streptococcus mutans, *a member of this group associated with dental caries which might be expected to be commonly associated with endocarditis, has only rarely been reported. This is possibly because of difficulties in isolation and identification. Differing blood culture media may affect the chances of isolation of these organisms, and, though brain-heart infusion, thiol, tryptic soy, and glucose-brain infusion broths have all proved satisfactory, subcultures may require increased CO_2 concentrations for growth. Pleomorphism in the resultant colonies and in the individual organisms may give rise to a hazardous misinterpretation of this appearance as contamination.* Strep. mutans *and the similarly penicillin sensitive* Strep. bovis *may be differentiated from the penicillin resistant enterococci by their lincomycin sensitivity and intolerance of 6·3 per cent sodium chloride. Precise differentiation of streptococci in bacterial endocarditis is of value both epidemiologically and in the management of the disease.*

The viridans group of streptococci are recognised as the commonest organisms associated with infective endocarditis (Cates and Christie, 1951) and remain so despite the recent increase in endocarditis caused by other organisms (Lerner and Weinstein, 1966). The group comprises six main species: *Streptococcus sanguis, Strep. mutans, Strep. mitis, Strep. salivarius, Strep. milleri,* and *Strep. pneumoniae. Strep. mutans* is a member of the microflora of the mouth and first achieved significance when described as an aetiological agent in the production of dental caries (Kilian Clarke, 1924). In 1928 Abercrombie and Scott described endocarditis caused by *Strep. mutans* and recent reports (Harder *et al.*, 1974; Parker and Ball, 1976) indicate that 6 to 14 per cent of cases of streptococcal endocarditis result from infection with this organism. The rarity of reports of isolation of this organism may be accounted for by difficulty in accurately identifying it. Three further cases of *Strep. mutans* endocarditis occurring in one year in a general hospital are reported here, with a discussion of the cultural characteristics of this organism.

Case reports

CASE 1

A 55-year-old man was admitted in January 1974 with a two-week history of fever, dating from a dental scale and polish. He gave a history of rheumatic fever at the age of 18 and of infective endocarditis at the age of 45, treated successfully with penicillin and streptomycin; he then had signs of mitral regurgitation. On examination, he was febrile (38°C) and there were subungual splinter haemorrhages. He had atrial fibrillation, signs of moderate mitral regurgitation, and an aortic early diastolic murmur at the left sternal edge. The white blood cell count was $7\cdot4 \times 10^9$/l and ESR 15 mm in the first hour. Urinalysis showed no abnormality. *Strep. mutans* was isolated from 9 blood cultures. He was treated with benzylpenicillin 3 M units 6-hourly intravenously for 3 weeks, followed by phenoxymethyl penicillin 500 mg 6-hourly by mouth with probenecid for a further 3 weeks, and made a rapid and complete recovery. The patient's serum was bactericidal at dilutions between 1/32 and more than 1/512 on intravenous treatment, and inhibitory at dilutions between 1/16 and 1/128 on oral treatment. The minimum inhibiting concentration of benzylpenicillin was 0·03 g/ml, and the peak serum level of benzylpenicillin was 18 µg/ml.

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CASE 2

A 42-year-old woman was admitted in April 1973 with a 2-week history of fever, myalgia, and ankle oedema. She was known to have a heart murmur which was first detected when she was 25. On examination, she was febrile, the spleen was enlarged, and there were signs of mitral regurgitation. A digital Osler's node developed a few days later. The white blood cell count was $6 \cdot 0 \times 10^9$/l and ESR 58 mm in the first hour. Urinalysis showed no abnormality. Blood cultures yielded an organism initially thought to be a *Corynebacterium*, but which was later identified as *Strep. mutans*. She was treated with benzylpenicillin 1 M units 4-hourly intravenously for 14 days, followed by phenoxymethyl penicillin 1 g 6-hourly by mouth with probenecid for 10 weeks, and also streptomycin 1 g daily by intramuscular injection for the first 4 weeks, and made a complete and uncomplicated recovery. The patient's serum was inhibitory to the isolated organism at dilution of 1/24 while she was receiving oral penicillin and streptomycin. The minimum inhibitory concentration benzylpenicillin was 0·12 μg/ml.

CASE 3

A 38-year-old man was admitted in November 1973. He had been ill for 4 months with night sweats, intermittent fever, and weight loss. There was a past history of exemption from National Service on account of a cardiac lesion. He gave no history of rheumatic fever. On examination he was pale and febrile (38·5°C), and there were signs of mitral regurgitation. The white blood cell count was $9 \cdot 6 \times 10^9$/l, and ESR 9 mm in the first hour; urinalysis showed microscopic haematuria. Four blood cultures yielded a growth of *Strep. mutans*. Treatment with benzylpenicillin 5 M units 6-hourly intravenously with probenecid for 9 days, followed by phenoxymethyl penicillin 500 mg 6-hourly by mouth with probenecid for 4 weeks, resulted in clinical cure. The ESR remained high and phenoxymethyl penicillin 500 mg 6-hourly by mouth was continued for a further 4 weeks. While on intravenous treatment the patient's serum was bactericidal to the isolated *Strep. mutans* at dilutions between 1/1024 and 1/4096, the minimum inhibitory concentration of benzyl penicillin being 0·007 μg/ml.

Discussion

The mouth supports an extensive microflora, *Streptococcus, Staphylococcus, Veillonella,* and *Neisseria* species being constantly present. *Actinomyces, Bacteroides, Corynebacterium, Fusobacterium, Leptotrichia,* and *Nocardia* species are also commonly found. Despite this wide variety of species, the viridans groups of streptococci appear to be the only oral commensals commonly implicated in the production of infective endocarditis. In their classic study, Cates and Christie (1951) found that this group was responsible for 95 per cent of cases of infective endocarditis. Recently there has been an increase in the number of cases caused by other organisms, notably *Staphylococcus aureus* and *albus* (Lerner and Weinstein, 1966), in association with cardiac surgery, renal dialysis, and drug addiction, but the number of cases of viridans endocarditis appears to be little changed. *Strep. mutans* has been found in 3 cases of endocarditis in a large general hospital in a 10-month period, endorsing the findings of Harder *et al.* (1974) who reported 9 patients with *Strep. mutans* endocarditis, representing 6 per cent of all cases of streptococcal endocarditis seen at the Mayo Clinic between 1966 and 1973. In a recent British study of streptococcal endocarditis, there was a similar (14%) incidence of disease caused by *Strep. mutans* (Parker and Ball, 1976).

In view of the frequency of these isolations it is relevant to ask why this organism is not being recognised more often. We believe that this is the result of difficulties in isolation and identification of *Strep. mutans*. Routine blood culture media vary in composition and may not all be suitable for this organism: in case 1 above, though all 9 blood cultures in brain-heart infusion broth yielded *Strep. mutans*, only 1 of a simultaneous series of cultures in a commercially produced Robertson's cooked meat broth yielded the organism. Glucose-brain infusion broth, tryptic soy broth, and thiol broth have all been found to be satisfactory for the growth of *Strep. mutans* from blood cultures (Harder *et al.*, 1974) and we have used brain-heart infusion broth successfully. Cultures must be maintained for three weeks and regularly subcultured on to horse-blood agar, in 5 to 10 per cent CO_2 and in anaerobic conditions with increased CO_2. The dependence of *Strep. mutans* on CO_2 suggests that it should be used in blood culture bottles. Colonies of this organism on blood agar are dry, adherent, and generally non-haemolytic. At low *p*H *Strep. mutans* may be bacillary resembling diphtheroids (Kilian Clarke, 1924), and variation in colonial morphology may lead to a mixed culture appearance. *Strep. mutans* may be incorrectly identified as an enterococcus, diphtheroid, or lactobacillus, and may be reported as *Strep. viridans* or a microaerophilic streptococcus. The pleomorphism shown by this organism may result in erroneous interpretation of blood cultures, and disastrous results for the patient may

Table *Differentiation of* Strep. mutans *and* Strep. bovis *from enterococci and* Strep. mutans *from other members of the viridans group*

	Strep. mutans	Strep. bovis	*Other* Strep. viridans	*Enterococcus* (Strep. faecalis *and others*)
Tolerance of 6·5 per cent NaCl	—	—	—	+
Lincomycin sensitivity	Sensitive	Sensitive	Sensitive	Resistant
Survival at 60° for 30 min	—	—	—	+
Growth in *p*H 9·6	—	—	—	+
Acid production from sorbitol	+	—	—	+
Acid production from mannitol	+	Variable	—	+

follow if it is thought to be a contaminant and treatment withheld.

Full criteria for the identification of *Strep. mutans* and details of the test techniques are described in a recent extensive study of the streptococci and aerococci associated with systemic infection in man (Parker and Ball, 1976). Some useful basic features which differentiate *Strep. mutans* and *Strep. bovis* from other enterococci, and *Strep. mutans* from other viridans organisms are shown in the Table. The *in vitro* sensitivity to lincomycin of the viridans group including *Strep. mutans* and of *Strep. bovis* is particularly useful in differentiating them from *Strep. faecalis* and other enterococci which are highly resistant.

Strep. mutans is found almost exclusively on teeth where it is a major component of dental plaque (MacLean, 1927) and it follows that removal of dental plaque and other minor dental procedures may lead to bacteraemia and subsequent endocardial colonisation by this organism. The factors associated with the colonisation of endocardium by streptococci are largely unknown, but *Strep. mutans*, in common with *Strep. sanguis* and *Strep. bovis*, and some strains of *Strep. mitior* produce dextran. Elliot (1973) found that dextran was produced by only 9 per cent of streptococci isolated during post-dental extraction bacteraemia but by 34 per cent of streptococci isolated from cases of endocarditis, and suggested that dextran production might promote adhesion of these streptococci to heart valves. Of the 317 cases of streptococcal and aerococcal endocarditis investigated by the Streptococcal Reference Laboratory, 53 per cent were caused by organisms which typically produce dextran (Parker and Ball, 1976).

Precise differentiation of both *Strep. mutans* and *Strep. bovis* from other viridans streptococci and from enterococci is worth while, for epidemiological reasons, and also because of the different antibiotic sensitivities of these organisms. Both *Strep. mutans* and *Strep. bovis* are invariably sensitive to benzylpenicillin. However, animal studies suggest that a combination of benzylpenicillin and an aminoglycoside results in quicker eradication of even penicillin sensitive viridans organisms from cardiac vegetations (Sande and Irvin, 1974) and this combination is probably indicated as primary therapy in *Strep. mutans* endocarditis.

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Fibreoptic studies of the aortic valve in dogs

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The study describes a method for visualisation of the aortic valve in the intact animal using a non-obstructive endoscopic system. Clearing of blood from the field of vision is achieved by the rapid injection of saline during a period of asystole.

Attempts have been made since 1913 to visualise intracardiac structures endoscopically with only modest success. Clearly, the main problem is how to replace the blood with a transparent medium for a sufficient length of time in order to permit observation and photographic recording. Three distinct methods have been used to clear the blood from intracardiac structures: (a) direct contact between the endoscope and the structure under examination, (b) displacement of blood by a transparent chamber between the lens system and the object, (c) displacement of blood by a clear fluid injected under pressure.

Before the report of Carlens and Silander in 1961, endoscopy had been performed only on the surgically exposed heart. Carlens and Silander used an endoscope equipped with an inflatable balloon over the lens system to inspect the interior of the right atrium in the intact animal. In 1964 Silander reported the clinical use of this method in 7 patients. Using similar methods, Gamble and Innis (1967) extended the procedure to inspect the aortic valve and the interior of the left ventricle in dogs. The obstruction to the circulation caused by the inflated balloon is a limiting factor to the usefulness of this method.

Several investigators have used clear fluid injected under pressure to enable visualisation of intracardiac and aortic structures. Only Pinet *et al.* (1966) used this method in the intact animal and they emphasised the difficulties and traumatic nature of the method. There have been no further reports on the use of this technique over the past 10 years.

In this paper an account is given of studies of the aortic valve in dogs using a 3 mm fibreoptic endoscope introduced via a carotid arteriotomy. The important and perhaps crucial variation in technique has been significantly to reduce cardiac output before and during the rapid injection of saline above the aortic root. This has permitted clear observation of the aortic valve with an unmodified endoscope and has also permitted observations to be made at varying distances from the valve. Examples of still photographs are illustrated in the Fig.

Method

Dogs weighing 1134 to 1588 g were selected for study and were anaesthetised using morphine intravenously (3 mg/kg) and an α-chloralose/urethane mixture (urethane 1000 mg/kg α-chloralose 100 mg/kg). This method of anaesthesia usually resulted in a bradycardia of between 50 and 60 beats a minute. On occasion supplemental doses of prostigmine were administered to induce bradycardia. A cuffed endotracheal tube was inserted enabling the intrabronchial pressure to be varied. Acute rise in the intrabronchial pressure to between 40 and 60 cm of water has two effects: (a) the heart and aorta are squeezed and partially emptied, (b) the venous return is virtually stopped resulting in a drastic reduction in cardiac output. Nordenstrom (1960) has documented the use of this technique both in dogs and humans in order to increase the relative concentration of injected radiographic contrast media. Vagal stimulation was also used to induce a period of asystole. In practice the animals were often refractory to vagal stimulation, and in the later experiments this technique was discontinued. A 3 mm Olympus fibreoptic endoscope was introduced into the aorta via an arteriotomy in a carotid artery. A No. 9 French gauge NIH catheter was introduced via an arteriotomy in a femoral artery and its tip placed immediately above the aortic valve.

By means of raising the intrabronchial pressure

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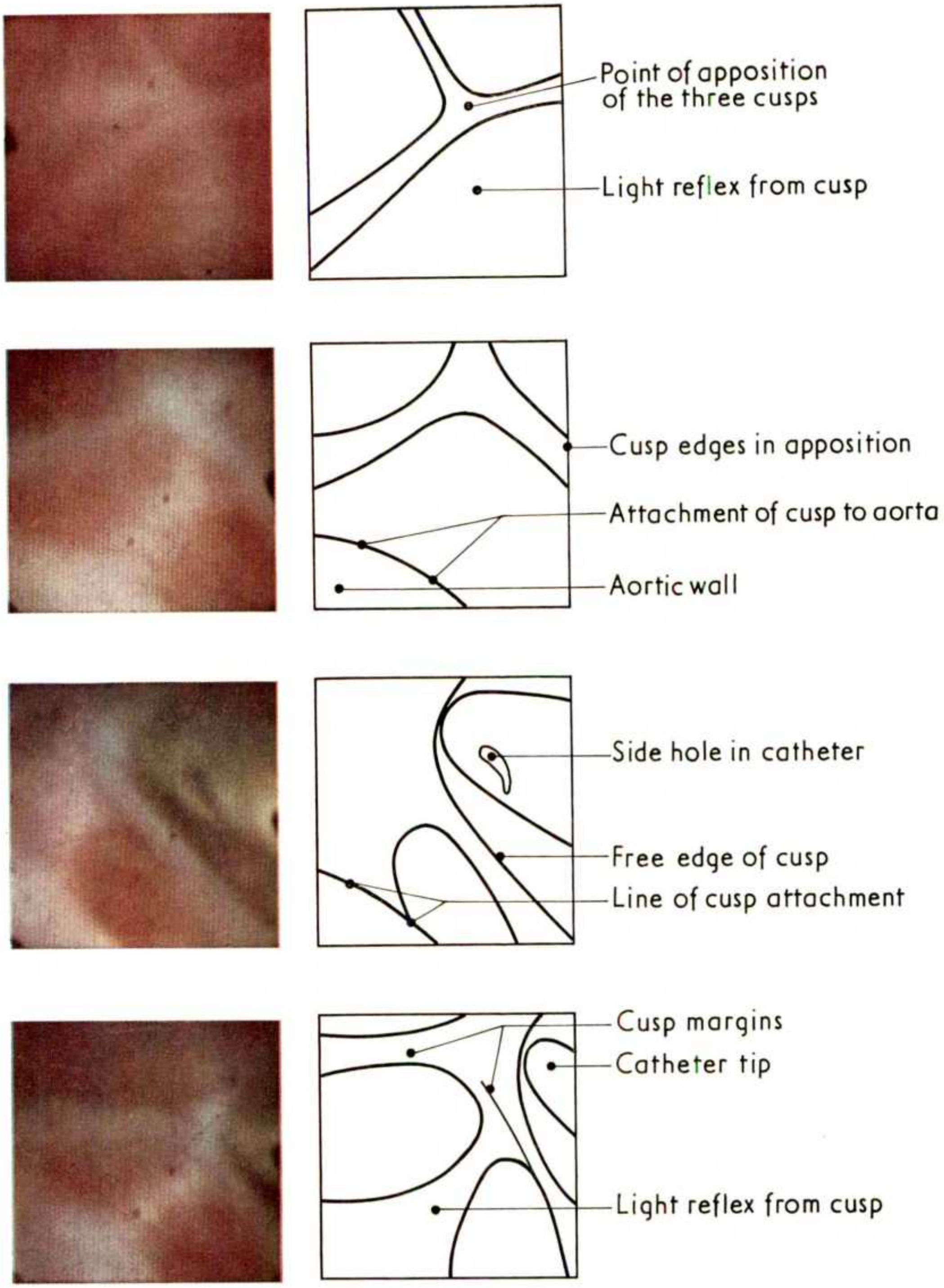

Fig. *Four views of the aortic valve as seen through a 3 mm fibreoptic scope. The hatching is the result of the arrangement of the fibre bundles.*

with or without vagal stimulation, asystole could usually be induced. Ninety ml normal saline were injected through the NIH catheter at a flow rate of 40 ml/s. The selection of such a large volume and flow rate was arbitrary and was close to the maximum attainable by the injection device used. Still photographs using Kodachrome II (ASA 80) or cine film using Kodak Ektachrome (ASA 60) were obtained during the transient period of clearing. The period of asystole could last from 5 to 15 seconds under normal circumstances. The dogs tolerated the procedure well and only 1 death was directly attributable to the examination out of some 8 experiments performed. In this instance the myocardium was perforated by the catheter and the animal succumbed in cardiac tamponade. The earlier experiments were somewhat compromised by the inadequacy of the standard light source, but the acquisition of an Olympus CLX high intensity light source has given greater latitude in camera work. Single plane fluoroscopy was used for catheter positioning and this meant that directional work with the endoscope was necessarily haphazard.

Discussion

The experiments described indicate that it is possible to achieve clear visualisation of the aortic valve with a non-obstructing endoscopic system provided that the cardiac output can be reduced drastically or stopped temporarily and that a rapid bolus of transparent fluid can be injected. It is important to have a significant reduction in heart rate even before acute methods to reduce cardiac output are applied. Experience showed that the tachycardia induced for example by pentobarbitone, resulted in problems with reducing the cardiac output. An increase in the intrabronchial pressure proved to be a very effective method of inducing asystole in the dog. Direct vagal stimulation was variable in its effect and was not as satisfactory as had been hoped. The standard endoscopic light source permitted only long film exposures and limited the distance from which one could observe the valve. The acquisition of a high intensity light source has enabled shorter exposure times and faster cine shutter speeds to be used as well as facilitating actual observation of the valve.

The present research has concentrated on the aortic valve in order to refine the techniques and equipment on an easily recognisable structure that could be readily localised.

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Ventricular haemangioendothelioma diagnosed in life

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A case of right ventricular outflow obstruction is described in which the electrocardiogram and chest x-ray film suggested a cardiac tumour. Cardiac catheterisation confirmed outflow obstruction and angiography showed a tumour. At operation a haemangioendothelioma was found.

Case report

A 10-year-old Libyan girl was referred because of effort dyspnoea. Her parents complained that she was smaller and less active than her sibs.

The patient looked well and was acyanotic. Her height was 1·32 m (15th centile) and weight 26·8 kg (3rd centile). The pulse was in sinus rhythm and normal in character. Blood pressure was 100/70 mmHg. Praecordial examination indicated moderate cardiac enlargement and a systolic thrill at the left sternal edge. The second sound was widely split, moving normally with respiration and there was an ejection murmur loudest in the pulmonary area. There was no ejection click.

The electrocardiogram (Fig. 1a) did not show right ventricular hypertrophy. It showed an abnormal axis of the mean frontal QRS vector (−140°) and an abnormal direction of the mean frontal T vector. The abnormal T vector suggested a myocardial lesion.

The chest *x*-ray film (Fig. 1b) showed moderate cardiac enlargement with normal lung fields. The echocardiogram showed a greatly thickened ventricular septum.

The physical signs were those of right ventricular outflow obstruction. The electrocardiogram indicated a myocardial lesion and the heart size on the chest *x*-ray film was large for the degree of obstruction judged to be present. A clinical diagnosis was made of right ventricular outflow obstruction and cardiac tumour.

Cardiac catheterisation (Table) confirmed right ventricular outflow obstruction. Left heart pressures were normal apart from a left ventricular end-diastolic pressure of 15 mmHg. Right ventricular angiography showed a filling defect in the outflow tract (Fig. 2a). Left ventricular angiography showed a filling defect in its left border (Fig. 2b). The left coronary artery was displaced upwards (Fig. 2c) and a tumour blush was seen beneath it.

The preoperative diagnosis was a tumour involving the right ventricular outflow, ventricular septum, and free wall of the left ventricle.

OPERATION

The heart was exposed through a median sternotomy. A tumour was found protruding from the anterior surface of the right ventricle extending to the lateral aspect of the left ventricle and around the origin of the pulmonary artery. The tumour was pink and nodular and had no capsule. It was firm and the cut surface bled freely. The surrounding myocardium was normal and the pericardium was not involved.

In view of the extent of the tumour, excision was not attempted. A biopsy was taken and the chest closed. The patient made an uneventful recovery.

HISTOLOGY

The tumour was highly cellular with a scanty fibrous tissue stroma (Fig. 3). Capillaries were visible in longtitudinal section and their presence was emphasised by reticulin staining. The tumour cells were the same as those lining the capillaries. The appearances were those of an haemangioendothelioma.

Discussion

Haemangioendotheliomata are composed of small vessels which show proliferation of the endothelial cells. This proliferation may obscure the vascular nature of the tumour. However, the basic structure can be seen by reticulin staining.

It is uncommon for this tumour to arise in the heart. Within the heart the right atrium is the most frequent site, often with spread into the pericardium. Wider dissemination, especially to the lungs, may occur. Clinical presentation may be as tamponade resulting from obliteration of the pericardial cavity by tumour (Sauerteig, 1958; Crenshaw, Dowling, and Cresswell, 1959) or

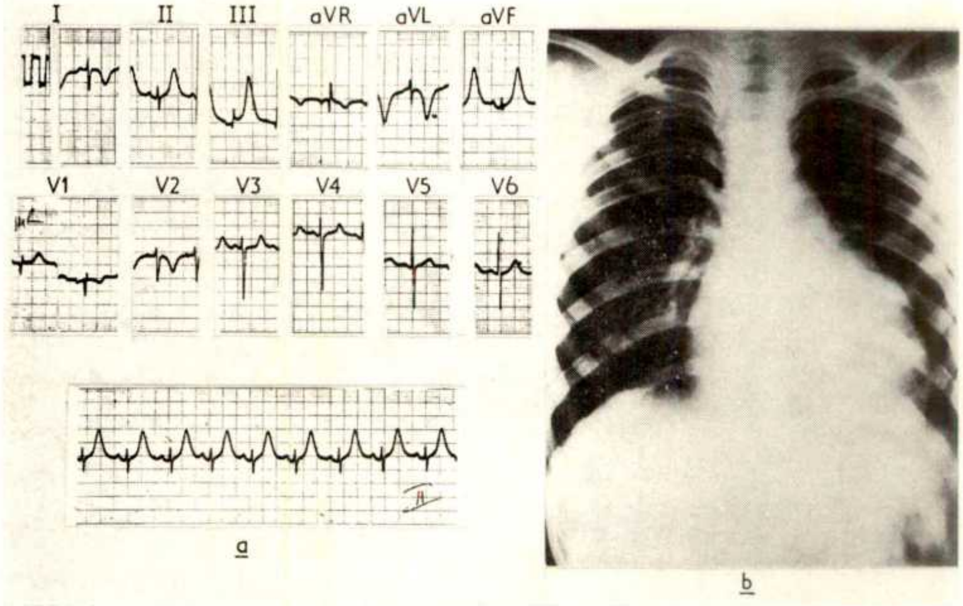

Fig. 1 *(a) Electrocardiogram, (b) posteroanterior chest x-ray film.*

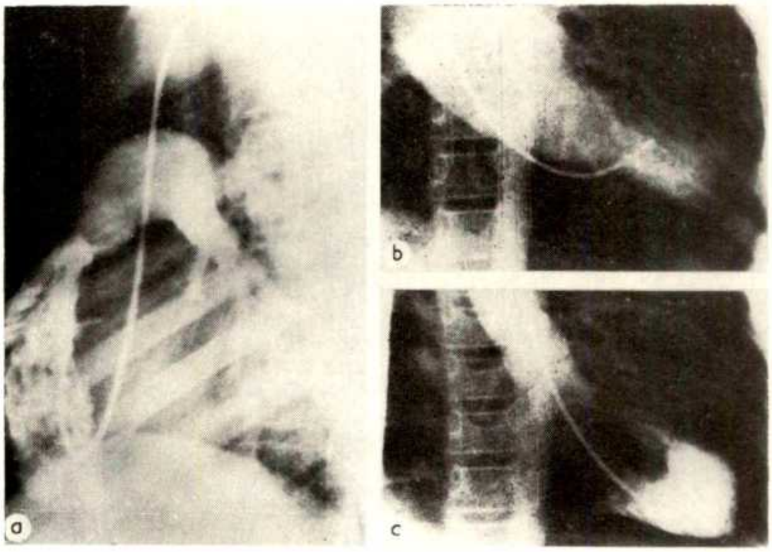

Fig. 2 *(a) Right ventriculogram, (b) left ventriculogram showing filling defect, (c) left ventriculogram showing displacement of the left coronary artery.*

Table *Cardiac catheterisation*

Site	*Pressure (mmHg)*
RV body	43/0
RV outflow	14/3
Pulmonary artery	14/10
Cardiac index	7·0 l/min per m²

haemopericardium (Tacket, Jones, and Kyle, 1950; Ito, 1964; Allaire *et al.*, 1964). Diagnosis in such cases has been at thoracotomy (Crenshaw *et al.*, 1959; Hansson *et al.*, 1970) or by pericardial aspiration (Tacket *et al.*, 1950). A right atrial haemangioendothelioma has been shown angiographically (Cheng and Sutton, 1955) with histological diagnosis at necropsy. Long-term survival has not been reported though temporary palliation of haemopericardium has been achieved with radiotherapy and cyclophosphamide (Allaire *et al.*, 1964).

The case described in this report is unusual; those previously reported have been in adults, and primary ventricular involvement is rare. At the time of writing, nine months after diagnosis, the patient remains well and the electrocardiogram and chest *x*-ray film are unchanged. Histological distinction between benign and malignant tumours of this type is difficult. Though the pericardium was not involved and there was no evidence of distant spread, the prognosis remains uncertain.

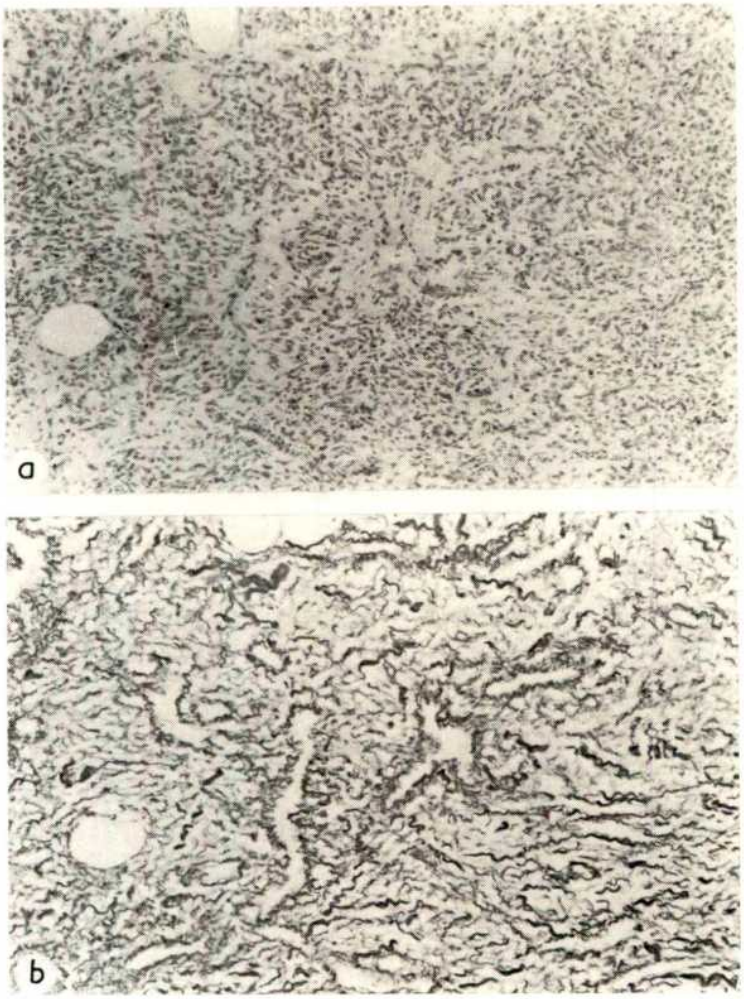

Fig. 3 *Histology of biopsy specimen. Corresponding fields (×120). (a) (H. and E.), (b) reticulin staining.*

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Escape-capture bigeminy in rate dependent (phase 3) block of atrioventricular conduction

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A specific, hitherto unpublished mechanism of escape-capture bigeminy based on rate dependent (phase 3) block of atrioventricular conduction is described.

Escape-capture bigeminy is a bigeminal rhythm in which each escape beat is followed by a conducted beat. Bradley and Marriott (1958) were the first to describe this interesting electrocardiographic pattern in a case of sinoatrial block. Schamroth and Dubb (1965) reported cases of escape-capture bigeminy resulting from sinoatrial block, atrioventricular block, and a second degree Wenckebach type atrioventricular block ending in an atrial echo beat. A fourth mechanism was published by Dubb and Schamroth (1975) in which escape-capture bigeminy was caused by blocked atrial extrasystoles. We present a case of escape-capture bigeminy caused by a specific, hitherto unpublished mechanism.

Case report

A 73-year-old man with coronary heart disease was admitted with a history of retrosternal chest pain. No myocardial infarction could be proved. He received no cardioactive medication.

Electrocardiogram on admission showed sinus arrhythmia with left bundle-branch block and atrioventricular dissociation caused by advanced atrioventricular block. For a short period constant ratio of block with bigeminy could be seen after which the advanced atrioventricular block with varying ratio of block returned. One week after admission the atrioventricular conduction disturbance disappeared.

Fig. 1 shows sinus arrhythmia, second degree atrioventricular block, with varying ratio of block. Most of the sinus impulses are not transmitted to the ventricles. An escape rhythm is interrupted by sinus beats transmitted with normal or prolonged PR intervals. If a P wave follows the escape QRS complex closely, the next sinus impulse is conducted to the ventricles (5th, 12th, and 17th P waves). If the P wave falls just before or is concealed within the QRS complex of the escape beat (3rd, 8th, 10th, and 20th P waves), the following P is not conducted to the ventricles. Fig. 2 shows an escape-capture bigeminy pattern. At an altered sinus and escape frequency the preceding P wave of the conducted sinus impulse follows closely (3rd and 6th P waves) or is concealed within (9th and 12th P waves) the QRS complex of the escape.

Discussion

Frequency dependency of the impulse conducting structures of the heart is a proved electrophysiological phenomenon (Mendez, Gruhzit, and Moe, 1956). The functional behaviour of the atrioventricular junction and His-Purkinje system both in the antegrade and retrograde direction has been extensively studied in clinical electrophysiology (Akhtar *et al.*, 1975). Our case is a specific manifestation of an atrioventricular block based on frequency dependency of the atrioventricular conduction (Moe, Childers, and Merideth, 1968). The two special characteristics of the case are the following: (1) The electrocardiographic pattern was induced by a bidirectional stimulation of the blocking zone. (2) At a given ratio of the sinus and escape frequency escape-capture bigeminy occurred.

It is apparent from the ladder diagrams that the atrioventricular conduction of the sinus beats is not accidental but follows the rule of rate dependency. Atrioventricular conduction can only occur if two consecutive stimuli arriving at the blocking zone reach a critical time interval. This time interval must exceed the effective refractory period (ERP) of the region of block. If the interval be-

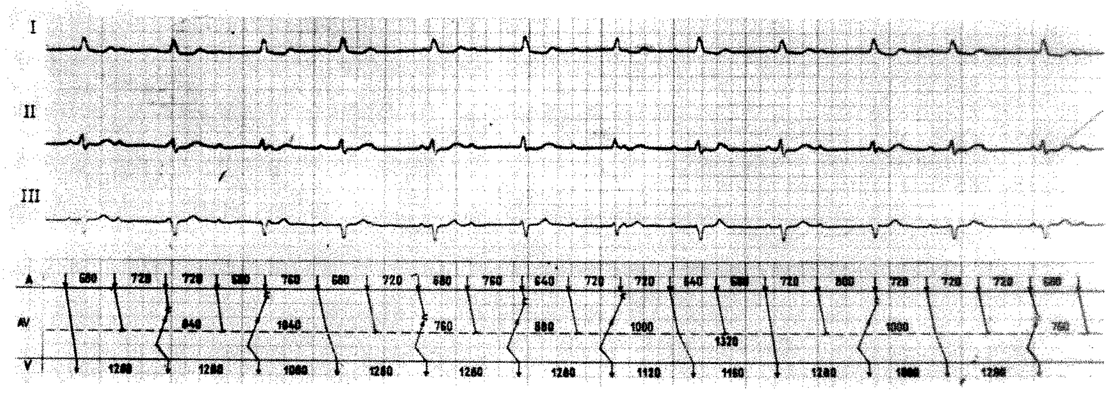

FIG. 1 *Rate dependent block of the atrioventricular conduction. Dotted line represents the blocking zone.*

tween two consecutive impulses is below the critical time, the second impulse is blocked. The interval between two sinus impulses is always shorter than the ERP of the blocking zone. Had the blocking zone not been stimulated by any other stimulus, regular 2:1 atrioventricular block would have occurred. In our case the region of block is depolarized by stimuli of escape origin too, changing the sequence of stimulation and the atrioventricular blocking ratio. The propagation of an atrial impulse to the ventricles becomes—in a peculiar way—strictly dependent on a proper time relation of an atrial impulse to the discharge of the escape pacemaker. The escape impulse depolarizes the blocking zone before the corresponding sinus impulse could have reached it. The concealed retrograde conduction of the escape beat prevents this sinus impulse from reaching and stimulating the blocking zone. Thus the time interval of two consecutive stimuli reaching and activating the blocking zone will exceed that of the corresponding PP interval. If the P wave falls just before or into the escape QRS complex, the increase will be small. If the escape QRS is followed by the P wave, this increase will be greater. In case of sinus arrhythmia the increase will also be influenced by the actual PP interval. When the critical simulus-stimulus interval in the blocking zone is reached, atrioventricular conduction will occur. The conduction of the 15th sinus impulse (Fig. 1) to the ventricles is somewhat different. After the prolonged atrioventricular conduction of the 13th P depolarization of the escape region is delayed, and the 15th P can reach the blocking zone before the next escape impulse. It seems likely that this complex picture can well be interpreted on the basis of rate dependency of atrioventricular conduction.

The basic mechanism of the escape-capture bigeminy shown in Fig. 2 appears to be the same. The time intervals between two stimuli arriving at the blocking zone are similarly increased by the escape beats. An altered sinus and escape frequency produced a situation where every third P wave was related to the escape QRS as described above. The augmented time interval of two stimuli at the blocking zone produced by the escape stimulus always exceeded the critical time interval. Thus, at this given ratio of the altered sinus and escape

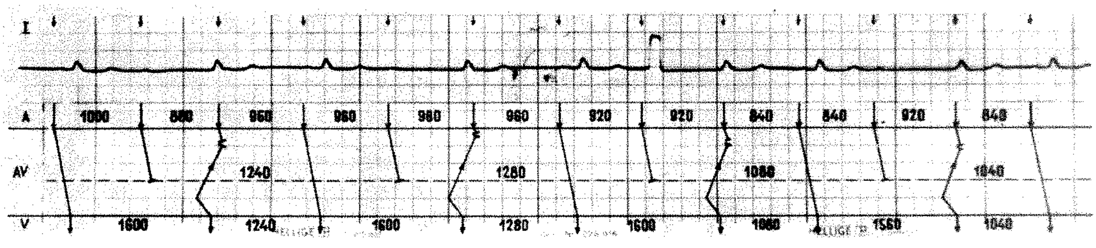

FIG. 2 *Escape-capture bigeminy.*

frequency the rate dependent atrioventricular block produced escape-capture bigeminy. As shown in Fig. 1 atrioventricular conduction is possible at a critical time interval of about 1000 ms; in Fig. 2 this proved to be 1040 ms. This shows a small variability of the ERP of the blocking zone. As the level of the blocking zone and that of the escape focus, the exit time, and anterograde and retrograde conduction velocity of the escape stimulus are unknown, the ERPs of the region of block in Fig. 1 and 2 reflect only proportional approximation of the real values. In our case the region of block and of the escape focus may be either in the atrioventricular junction or in the right bundle-branch.

Escape-capture bigeminy in frequency dependent atrioventricular block differs thoroughly from escape-capture bigeminy in stable second degree atrioventricular block. In the latter there is no cause-and-effect relation between the escape and conducted sinus impulse. In our case with rate dependent block of the atrioventricular conduction the changes produced by the escape impulse created the condition for the next sinus impulse to be transmitted.

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British Heart Journal, 1977, **39**, 469-470

Syphilitic ostial occlusion

S. HOLT

From Liverpool Regional Cardiac Centre, Liverpool

A patient presenting the picture of congestive cardiomyopathy was found to have syphilitic obliteration of the left coronary artery. Aortic regurgitation, angina, and myocardial infarction were notably absent.

Syphilitic stenosis or obliteration of the coronary ostia is a rare disease (Schrire *et al.*, 1966). Heggtveit (1964) reviewed the major clinical and pathological features of 100 cases of syphilitic aortitis derived from a necropsy series of 13 082 patients and found syphilitic coronary ostial stenosis or occlusion to be present in 26 cases. Bruenn (1934) analysed the clinicopathological findings in 118 cases of cardiovascular syphilis to define the role of syphilitic disease of the coronary arteries in relation to the general picture of cardiovascular syphilis. Of 118 cases described, 39 (33%) had coronary ostial stenosis. Of these 39 cases, 34 (87%) had aortic regurgitation; the right coronary ostium was found to be stenosed eight times more commonly than the left.

A patient with syphilitic obliteration of the left coronary ostium presented with clinical features suggesting a diagnosis of congestive cardiomyopathy.

Case report

A 49-year-old car mechanic complained of progressive exertional breathlessness for 6 weeks. He claimed previous good health and in particular denied any history of chest pain or excessive alcohol consumption. He showed oedema, raised venous pressure, sinus rhythm, and a blood pressure of 120/80 mmHg. The apical impulse was sustained, forceful, and displaced to the left, but there was no parasternal lift. There was a summation gallop but no sign of aortic or mitral valve disease. The jugular venous pressure was raised to 6 cm above the clavicle but showed a normal wave form. The electrocardiogram showed left ventricular hypertrophy with the pattern of left anterior hemiblock. The radiological cardiothoracic ratio was 65 per cent. The ascending aorta was prominent and no valvular or aortic calcification was visible. A diagnosis of myocardial disease of uncertain cause was made. The heart failure completely responded to treatment in hospital within two weeks.

Three months later, despite maintenance treatment, the fluid retention recurred, with symptoms of acute left ventricular failure but again without chest pain. Clinical examination at this stage indicated severe congestive cardiac failure with mild icterus. There was pronounced jugular venous engorgement with dominant V waves in the jugular venous pulse. A summation gallop rhythm was present and a midsystolic murmur was audible at the right sternal edge, which increased in intensity on deep inspiration, suggesting tricuspid valvular regurgitation. The electrocardiogram and chest film were unchanged. Persistent slight rise in serum aminotransferase enzymes was considered to reflect hepatic congestion. A pyruvate tolerance test gave a normal result. Blood cultures were repeatedly negative. Antinuclear factor was not detected and lupus erythematosus cells could not be seen. Serological tests for syphilis were found to be strongly positive, shortly before the patient's sudden death from asystole.

Necropsy showed syphilitic aortitis of the ascending aorta but a normal aortic valve. The left coronary ostium was totally obliterated by fibrous tissue and the left main coronary arterial lumen was narrow but patent 5 mm from the ostium (Fig.). The left coronary arterial branches showed no sign of atheroma or other occlusive disease. The right coronary ostium and artery were large and healthy. There was no histological evidence of syphilitic periarteritis or endarteritis of the coronary arteries.

The heart was enlarged, weighed 620 g, and was hypertrophied with dilatation of the ventricle. There was moderate but widespread subendocardial fibrosis. Mural thrombi and amyloid material were absent. There was no evidence of syphilis outside the cardiovascular system.

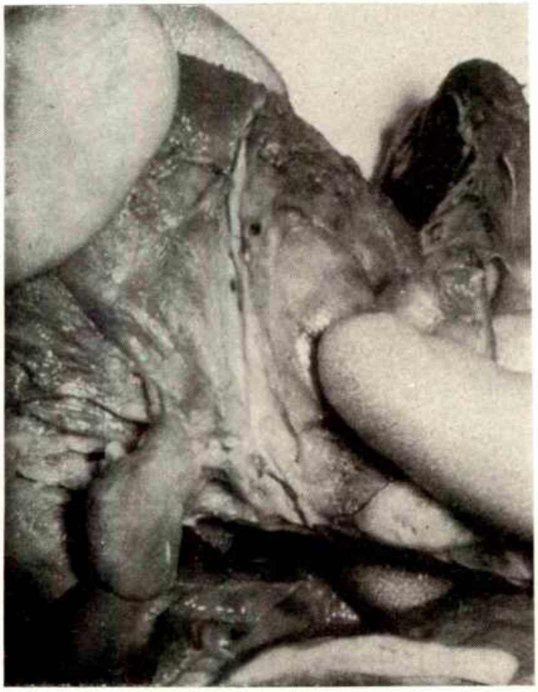

Fig. *The ostium of the coronary artery has been occluded by inflammatory tissue.*

Discussion

Syphilitic cardiovascular disease occurs more frequently than is recognised clinically. An accurate clinical diagnosis was established in only 17 per cent of a large group of cases of syphilitic aortitis reviewed in a clinicopathological necropsy study (Heggtveit, 1964). Beck *et al.* (1965) emphasised the importance of suspecting syphilitic ostial occlusion when angina is disproportionate in the presence of aortic regurgitation, but in this patient there was no history of angina pectoris and no clinical or necropsy evidence of aortic valve involvement. In Bruenn's series (1934) 62·5 per cent of cases with stenosed coronary ostia experienced cardiac pain, the inference being that the absence of angina pectoris does not rule out the presence of such stenosis.

Virtually all patients with luetic aortitis will have hearts which display some degree of interstitial fibrosis of the myocardium (Heggtveit, 1964). It is uncertain whether myocardial fibrosis in these cases results from ostial stenosis, or whether it is due to syphilitic myocarditis or coexistent coronary atherosclerosis. It seems likely that the subendocardial fibrosis seen in this patient was a significant factor causing progressive cardiac failure. The relation of ostial stenosis to so-called syphilitic myocardial disease is unclear (Warthin, 1922; Saphir and Scott, 1930; Storey, 1958). Since a large proportion of previously described cases was complicated by aortic regurgitation and coronary atheroma, it is difficult to assess the contribution of ostial stenosis to left ventricular hypertrophy and myocardial fibrosis. Congestive cardiac failure was found in 8 of 15 cases of syphilitic ostial stenosis (Love and Warner, 1934), and was even the presenting feature in 2, but it was not specified whether these patients had aortic regurgitation or coronary disease in addition. Heggtveit (1964) reports congestive heart failure in 7 of 11 patients with ostial stenosis without aortic regurgitation but only 3 of 11 had clinical cardiac enlargement and 2 had hypertension.

If coronary ostial stenosis or occlusion can give rise to myocardial failure, in the absence of aortic regurgitation, angina, and myocardial infarction, then this entity will need to be included in the differential diagnosis of congestive cardiomyopathy (Oakley, 1974), particularly in the younger adult.

I thank Dr. B. A. Walker for permission to report this patient, Dr. F. Whitwell for supplying post-mortem details and the photograph, and Dr. E. J. Epstein and Dr. A. Harley for assistance in preparing the paper.

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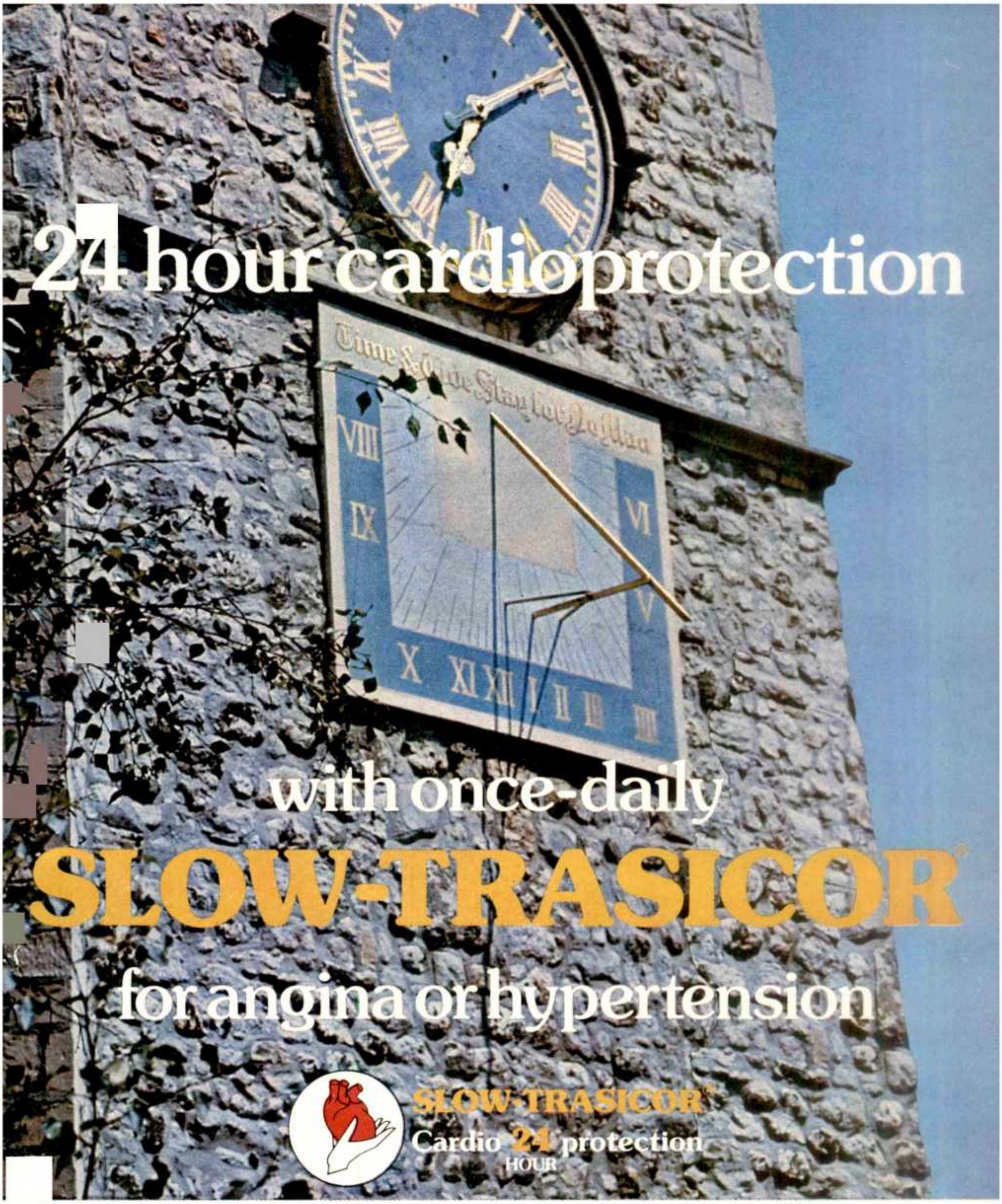

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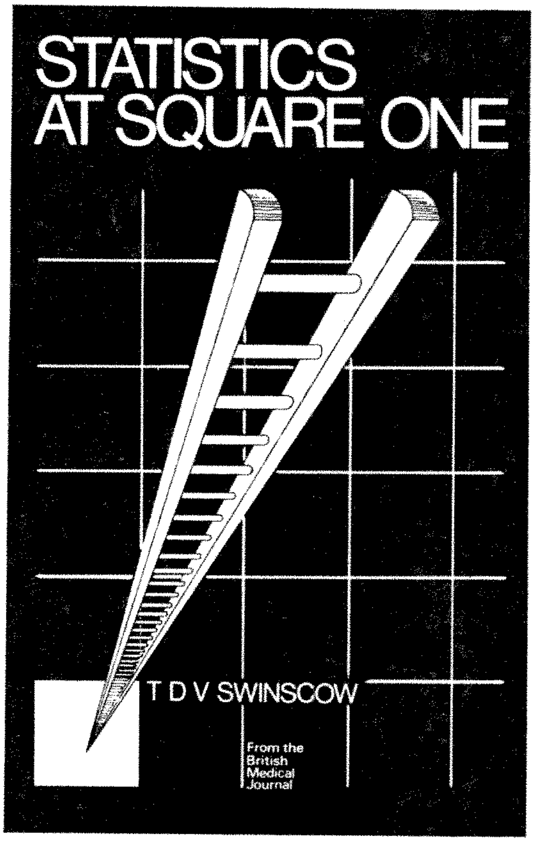

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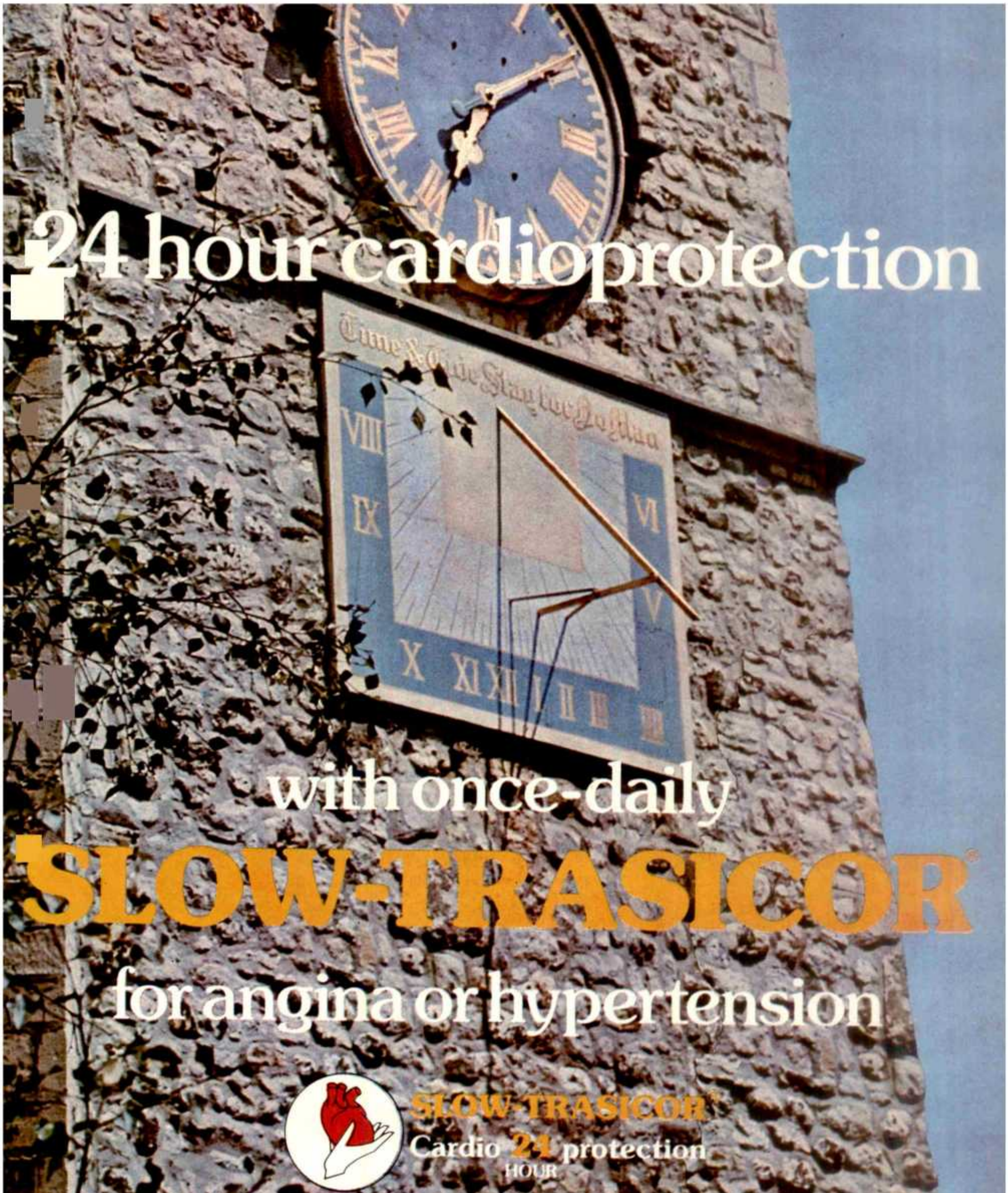
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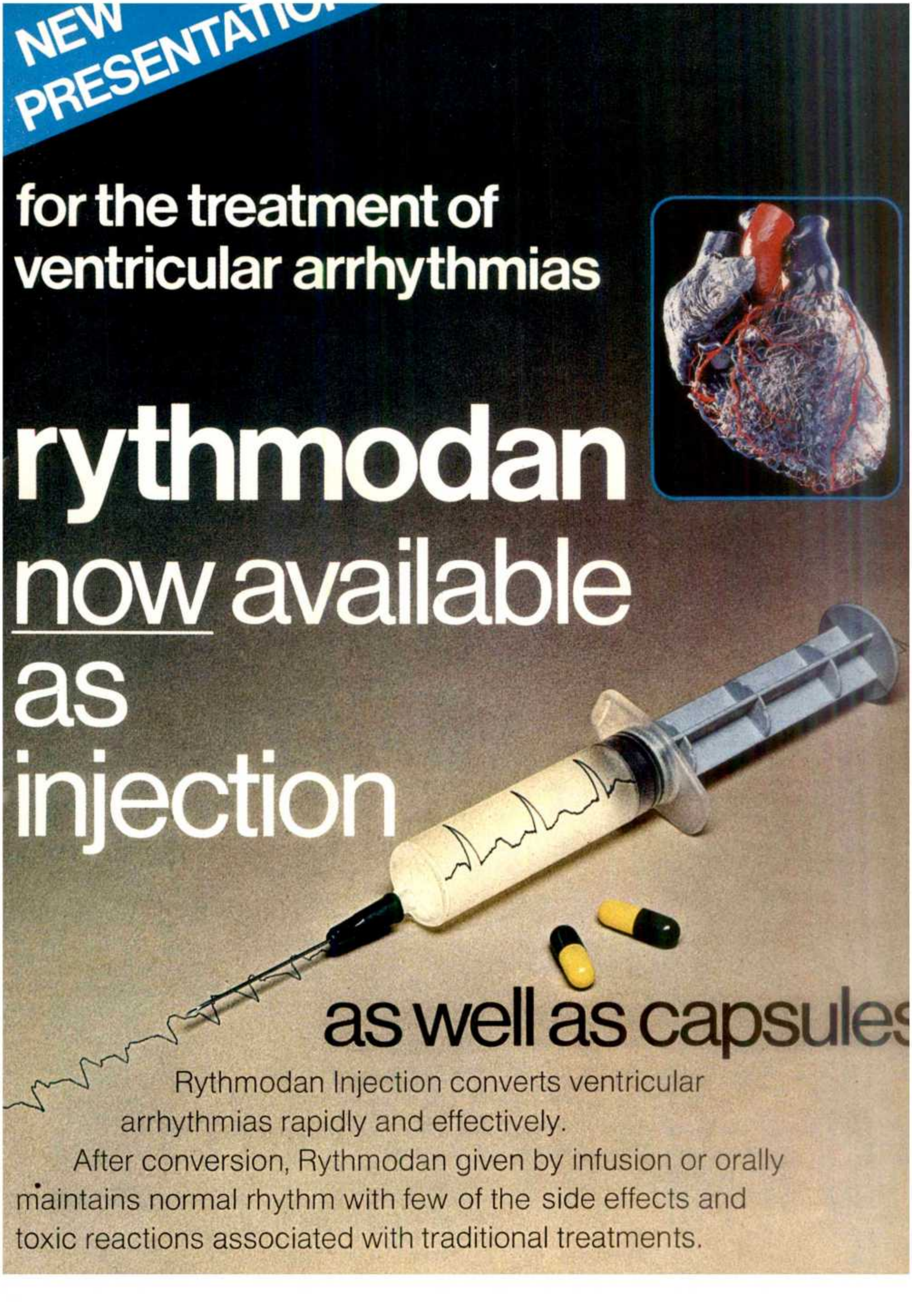NEW
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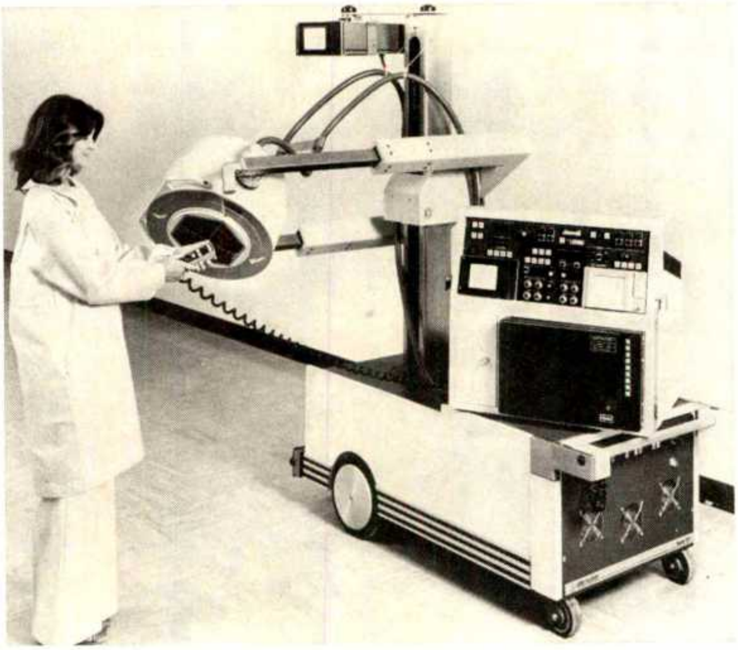

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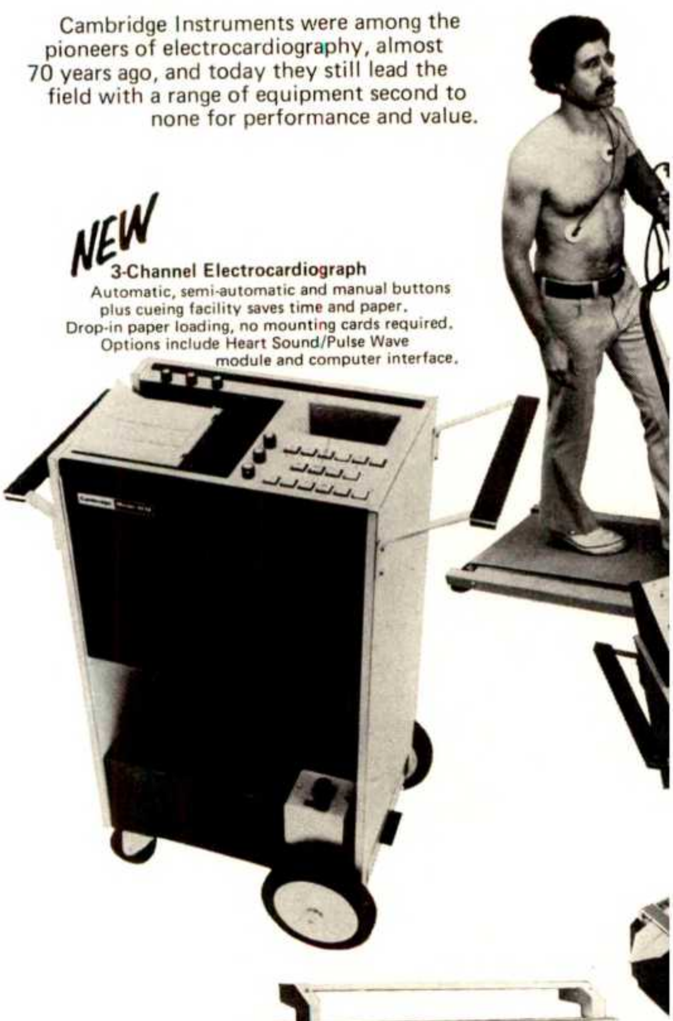

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ADRENOCEPTOR BLOCKADE
E USE OF TRANDATE IS BEING MONITORED IN THE UNITED KINGDOM

IN PRINCIPLE

n essential hypertension, the peripheral resistance increased and the cardiac output normal. The ost desirable way to lower blood pressure is, herefore, to decrease the peripheral resistance and ot adversely affect cardiac function. Unfortunately, he available antihypertensive drugs which reduce eripheral resistance by impairing sympathetic erve activity or by other means, cause side ffects that are unpleasant to patients.

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his beta-blockade protects the heart from the eflex sympathetic drive normally induced by peripheral vasodilatation and so the reduction in lood pressure is achieved without cardiac stimuation. Conversely increased reflex activity moduates the beta-blocking effect of the drug on the eart and the resting cardiac output is not ignificantly changed.

he resultant effects of TRANDATE are that the lood pressure is decreased, the cardiac output s maintained at rest and after moderate exercise, and the baroreflexes remain sufficiently ctive to avoid side effects associated with postural ypotension in most patients.

A further advantage of TRANDATE is that it does ot cause the sedation or lethargy often associated

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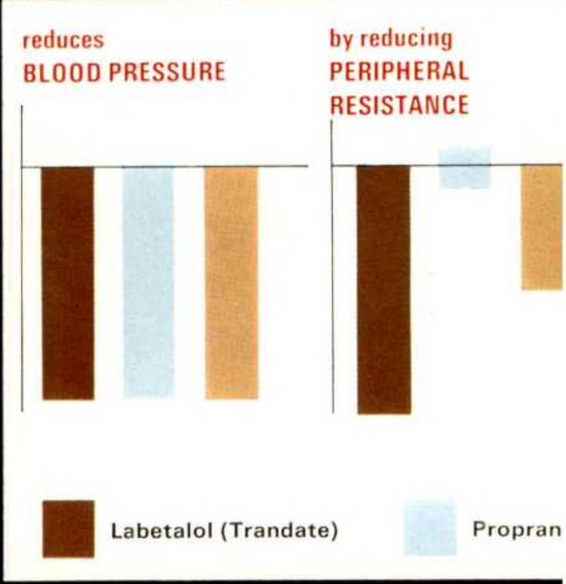

Diagram to illustrate the unique p

"It (Trandate) is an effective hypotensive ag
that appears capable of controlling the bl
pressure in patients that previously needed la
doses of drugs such as methyldopa."

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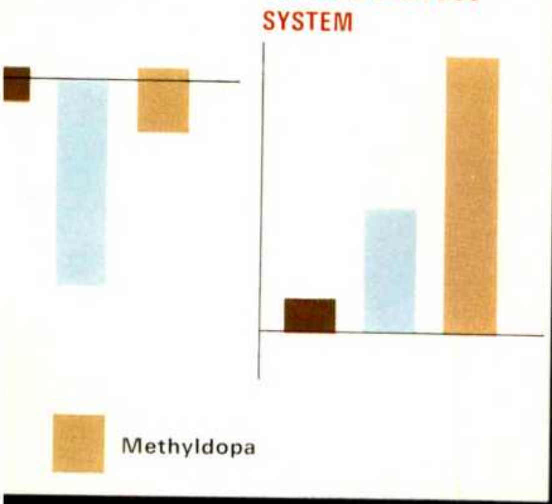
HYPERTENSIVE

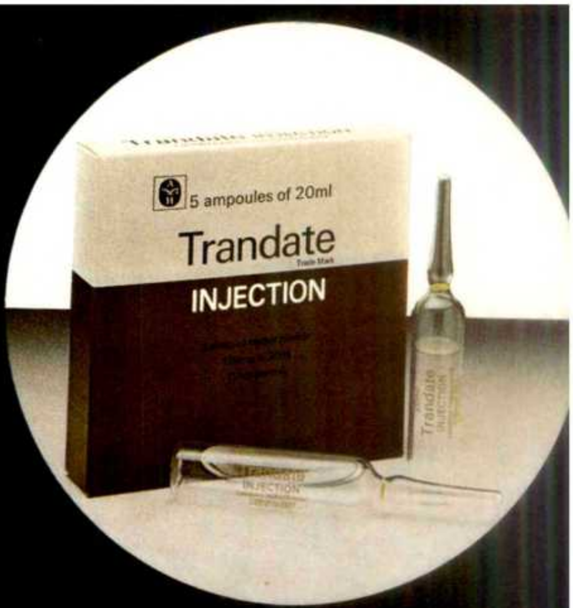
rmal circulation



ction of Trandate in hypertension.

> *etalol is an attractive compound for clinical nd there can be little doubt that there is an rtant place for it in the clinician's armamen- n."*

Joekes, A.M. & Thompson, F.D. (1976) *Brit. J. clin. Pharmacol.*, **3** (Suppl. 3), 789.



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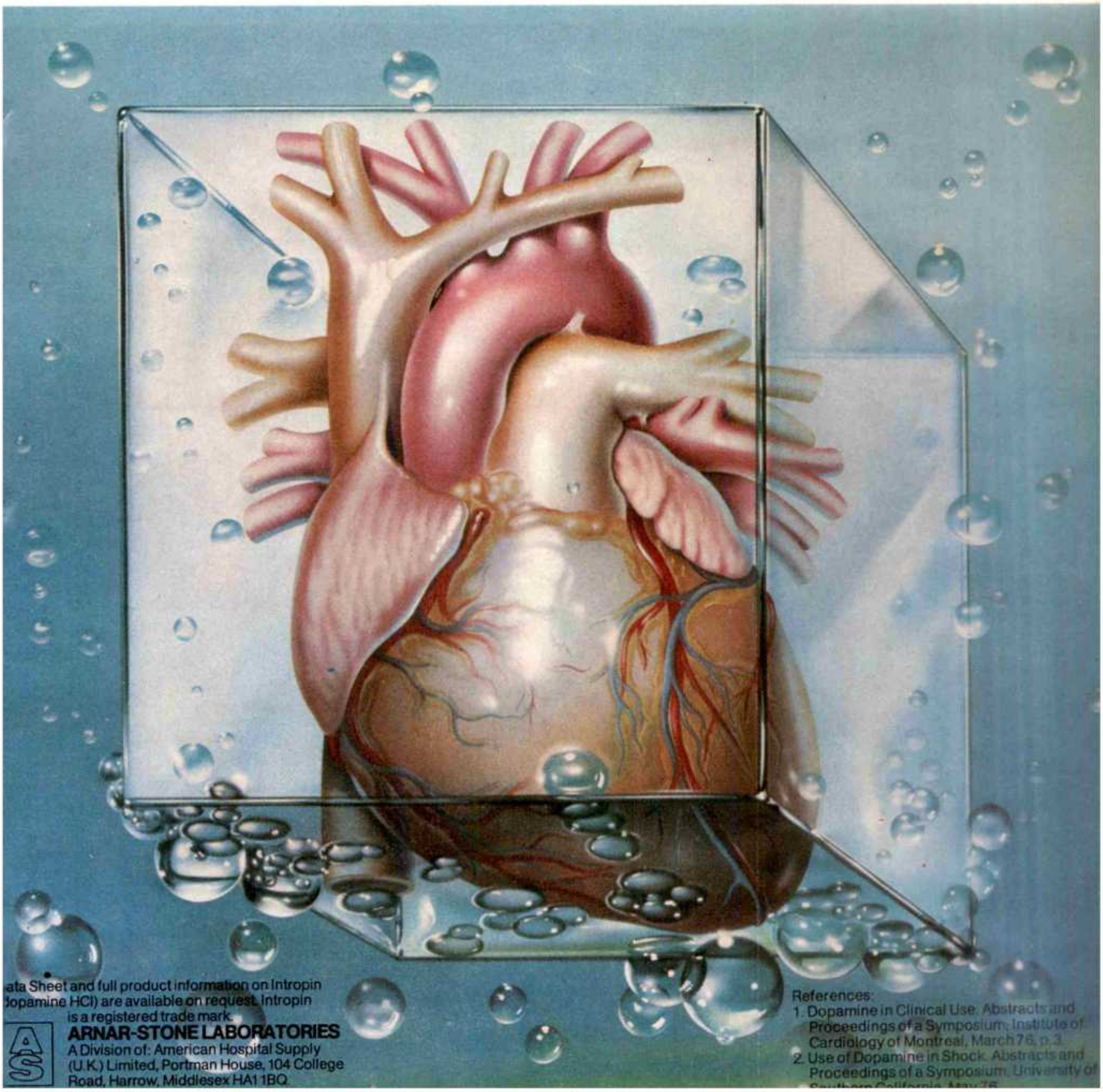

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1. Dopamine in Clinical Use. Abstracts and Proceedings of a Symposium, Institute of Cardiology of Montreal, March 76, p.3.
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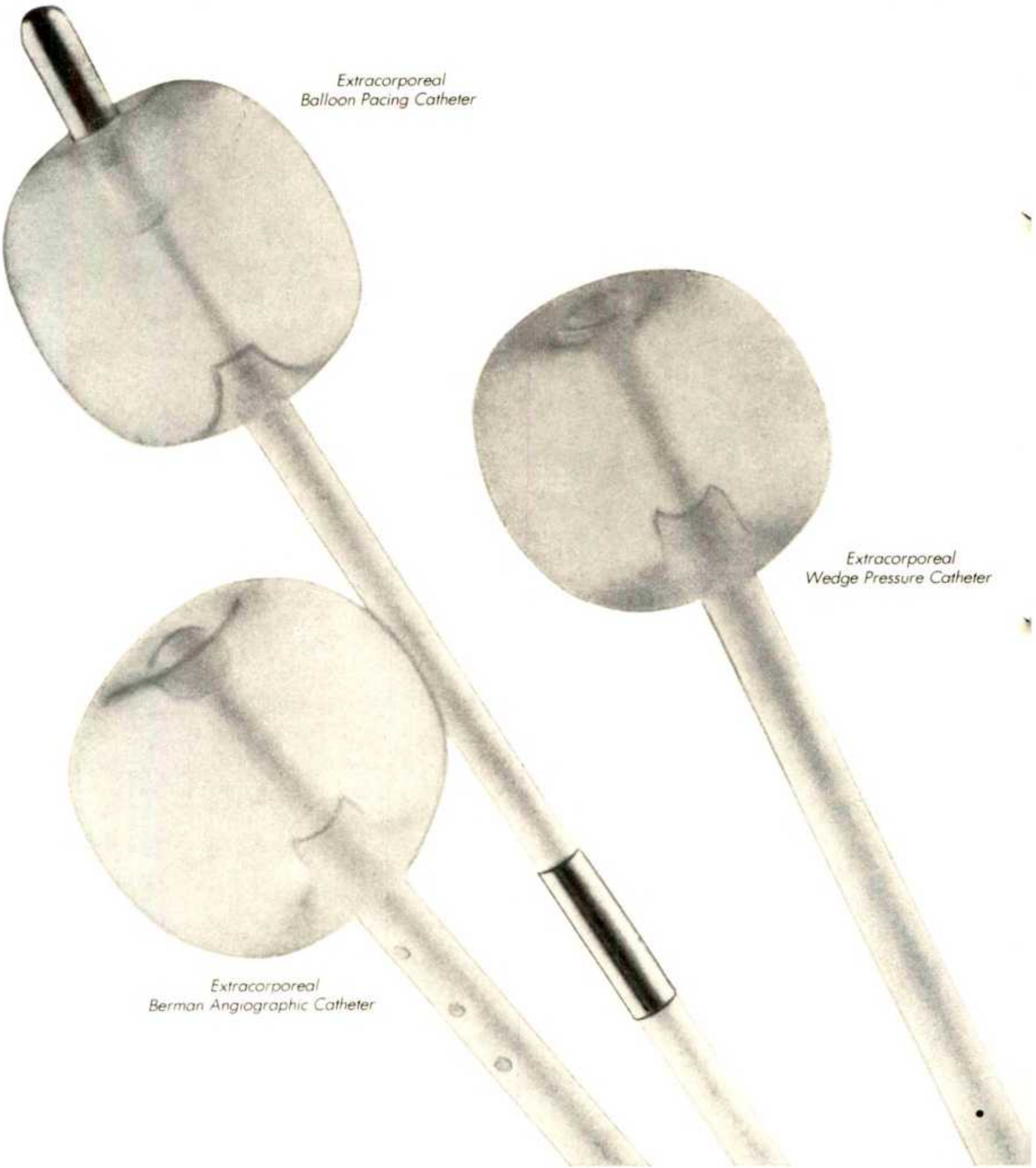

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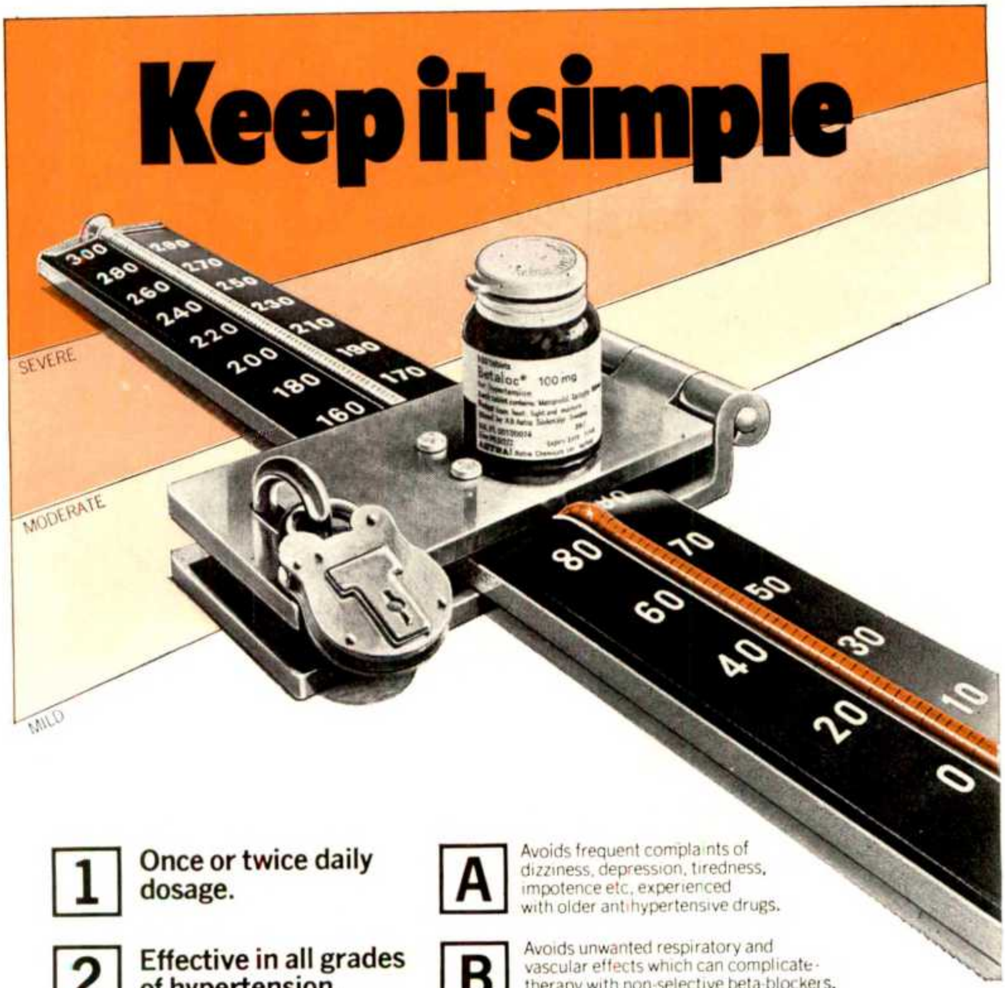

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British Heart Journal, 1977, **39**, 471–476

Rapid mobilisation after acute myocardial infarction
First step in rehabilitation and secondary prevention

P. E. THORNLEY AND R. W. D. TURNER

From the Chest Unit, City Hospital, Edinburgh, and the Western General Hospital, Edinburgh

Rapid mobilisation after acute myocardial infarction as the first step in a planned programme of rehabilitation and secondary prevention was studied in a group of 142 men under 65 years of age admitted to a coronary care unit.

Patients without complications were mobilised after 2 days' bed rest, but the programme was flexible and those with complications were mobilised less rapidly. Fifteen patients died before mobilisation could be started. In 127 who survived long enough to be mobilised, 74 (58%) spent 2 to 4 days in bed, 42 (33%) 5 to 10 days, and 11 (9%) more than 10 days. The mean period of bed rest was 5·4 days.

Rapid mobilisation eliminated the need for physiotherapy and led to early discharge from hospital with more economic use of hospital beds. In 125 patients who were discharged, 99 (79%) had 16 days or less (5 to 16) in hospital. The mean period of hospital stay was 15·5 days.

A programme of progressive rehabilitation with advice on secondary prevention, which was started in hospital, was continued at a convalescent hospital with graded exercises supervised by physiotherapists. This allayed anxiety and led to a more confident return home. A community nurse visited the home to reinforce advice given in hospital to the patient and his wife and extend primary prevention to the family. Review was undertaken at a special clinic to ensure the safety of the programme and to give further reassurance and advice about early return to work, exercise, and secondary prevention. Cardiac neurosis was thereby virtually prevented. In 105 eligible for employment, 46 per cent had returned to work within 12 weeks and 86 per cent within 24 weeks, of whom 90 per cent returned to their former employment.

In 127 patients who had been mobilised, 3 (2·5%) died within 6 weeks, and a further 8 (6·5%) had various nonfatal cardiac complications, but none of the 74 mobilised rapidly after 2 to 4 days died within this period. Only one was readmitted within 4 weeks.

In view of this and other reported experiences, it is clear that rapid mobilisation and early discharge after myocardial infarction should now be standard practice and there is no need of further evidence of its safety.

As recently as 1969, a 3-week period of bed rest after myocardial infarction was accepted practice in Britain (*Lancet*, 1969). Since then there has been a trend toward faster mobilisation and earlier discharge from hospital, but practice still varies widely (Heasman and Carstairs, 1971) even between physicians in the same hospital (Duke, 1971). In 1973 patients in a Glasgow hospital had 7 days in bed and 3 weeks in hospital (Medical Division, Royal Infirmary, Glasgow, 1973), in Stoke on Trent 1 day in bed and 8 days in hospital (Tucker *et al.*, 1973), while Datey in Bombay allowed only 25 per cent of survivors of acute infarction to walk 30 yards after 2 weeks (Datey *et al.*, 1973).

Received for publication 16 August 1976

It is unusual for British physicians to supervise later rehabilitation or secondary prevention after discharge from hospital (Royal College of Physicians, 1975). In 1971, in answer to a questionnaire, 113 members of the British Cardiac Society stated that they were in favour of some form of rehabilitation service, but 80 had no facilities (Groden *et al.*, 1971).

This variation in practice, which generally does not include full rehabilitation, led us to examine the results of our method of rapid mobilisation linked to a planned programme of continued rehabilitation and secondary prevention. The method was simple and did not require elaborate facilities. Other advantages included a short hospital stay, confident return home, early return to work, and prevention of cardiac neurosis.

Hurst in a recent Editorial (Hurst, 1975) pointed out the importance of considering all patients, with and without complications and including deaths, in any analysis of early ambulation and that many who do have complications, unless severe, benefit from early mobilisation. In this study all have been included.

Patients

One-hundred-and-forty-two men under the age of 65 were admitted under the care of one of the physicians in charge of the coronary care unit (CCU) of the Western General Hospital in Edinburgh. Myocardial infarction was diagnosed when there was a convincing history in the preceding 48 hours together with either (a) an acute rise to at least twice the normal upper limit of serum aspartate aminotransferase or serum lactic dehydrogenase, or (b) electrocardiographic changes of 'certain' or 'very probable' myocardial infarction by WHO criteria 1959 (World Health Organisation, 1959).

The mean age was 54·9 (36 to 64) years.

The delay between onset of symptoms and admission was less than 48 hours in all cases (mean 10·4 hours) and less than 8 hours in two-thirds of them.

The position of the infarct was anterior in 59 (42%), inferior in 34 (24%), posterior in 3 (2%), combined sited in 26 (18%), and unclassified in 20 (14%) because of bundle-branch block or incompletely evolved electrocardiographic abnormalities before death.

Seventy-two (51%) patients had a past history of coronary heart disease, 45 (30·5%) had stable angina, and 13 (9%) had had unstable angina in the preceding month.

Method

Admission was to a Coronary Care Unit with conventional facilities for monitoring and treatment of emergencies. Patients were under the care of the staff on duty while in the unit, but were subsequently discharged to a general ward under one of the physicians in rotation according to the day of admission. Consequently, each physician received patients admitted on different days of the week, resulting in effective randomisation. All patients in this series were under the charge of one physician (R.W.D.T.).

Initially all were treated in bed but allowed to wash, shave, and feed themselves and, unless too ill, to use a bedside commode. Warfarin was given for prophylaxis of venous thrombosis, unless contraindicated, but withdrawn as soon as the patient was ambulant. Patients free from cardiac pain, shock, hypotension, abnormal praecordial pulsation, significant cardiac failure or arrhythmia were allowed to sit in a chair after two days in bed. On the third day a few steps around the bed were allowed and after this they were permitted to walk freely about the ward until fully mobile. The programme of mobilisation was flexible and adjusted to individual need so that some with complications were mobilised more slowly.

During this time their medical condition was explained in simple terms. Wives were seen by a dietitian and given advice on a suitable calorie, low-saturated fat, and low-cholesterol diet with partial substitution by polyunsaturated fat and restriction of sugar. Smokers were advised dogmatically to stop. Each patient was given an explanatory booklet on coronary risk factors.

In addition, all patients were seen by a community nurse who acted as a link between hospital, home, and family doctor. She made further inquiries about the domestic and working situations and later made a home visit to reinforce advice given in hospital, answer questions, and extend advice to the family by way of primary prevention.

Usually, after 10 to 14 days, a two-week period in a convalescent hospital was recommended. Active rehabilitation with exercise to improve muscle tone and joint mobility, followed by progressive walking, was supervised by physiotherapists. Most were told they would probably be taking more exercise within a few months than for many years past.

On discharge from the convalescent hospital, review was undertaken at a special outpatient clinic, again after 3 months (or sooner if indicated), and thereafter at longer intervals. At each visit, after inquiring, a brief physical examination was made and blood taken for measurement of plasma lipids. An electrocardiogram and *x*-ray examination were carried out if indicated.

The purpose of continued supervision was to allay anxiety, ensure the safety of progressive activity and to encourage adherence to the secondary prevention regimen and early return to work.

Results

Information was complete on 140 of 142 patients; unfortunately, 2 were not given clinic appointments in error, and later they could not be traced.

MISCELLANEOUS FACTORS

Bed rest

Fifteen patients died while still confined to bed.

This left 127 to be mobilised; 74 (58%) had 2 to 4 days in bed, 27 (21%) 5 to 7 days, 15 (12%) 8 to 10 days, and 11 (9%) more than 10 days. The range was 2 to 33 days, with a mean of 5·4 days. Fifty-one were considered unfit for mobilisation before the 5th day because of arrhythmia (28), defect of conduction (9), cardiac pain (8), recurrent infarction (1), and cardiac failure (7).

Duration of hospital stay

Two patients died in hospital after mobilisation. Of the 125 discharged 86 (69%) were in hospital for 14 days or less. The range of hospital stay was 5 to 99 days, with a mean of 15·1 days (Table 1). The number of days in hospital was partly determined by the availability of a convalescent bed and, had one been available on the day required, 100 (86%) would have been transferred on the 12 to 14th day.

Convalescent hospital stay

One-hundred-and-four patients stayed in the convalescent hospital for a mean of 12·1 days. Six discharged themselves early and 3 had to be readmitted to the Coronary Care Unit. Twenty-one did not go to the convalescent hospital for a variety of reasons, which included patient refusal and long distance from home, making it inconvenient for relatives to visit them.

Time off work

Seven patients died within 24 weeks before returning to work, and 11 were retired or redundant before admission to hospital. Information was incomplete in two. In the remaining 105 eligible for return to work, 48 (46%) returned within 12 weeks, 73 (70%) within 16 weeks, and 90 (86%) within 24 weeks (Table 2).

In the 15 (14%) who had not returned to work within 24 weeks, 7 had angina or dyspnoea and 5 had previously been employed in heavy manual labour and were advised to change to less strenuous work but were unwilling to take alternative employment with less pay. There was no satisfactory reason for prolonged time off work in the remaining patient.

Table 1 *Length of stay in hospital*

Days in hospital	*5–12*	*13–14*	*15–16*	*> 16*	*Total*
No. of patients	49 (39%)	37 (30%)	13 (10%)	26 (21%)	125 (100%)

Table 2 *Length of stay off work*

Time off work (wk)	*< 8*	*9–12*	*13–16*	*17–24*	*> 24*	*Total*
No. of patients	17 (16%)	31 (30%)	25 (24%)	17 (16%)	15 (14%)	105 (100%)

Change of occupation

Of the 90 patients returning to work within 24 weeks, 81 (90%) resumed their former employment. The reason given for a change in occupation included the employer's offer of different work in 6, and advice from the hospital physician in 1. Two patients themselves decided that alternative work would be more suitable.

MORTALITY

Altogether 25 patients died within 24 weeks of the acute attack (17·6%). This included 15 who died within 16 days of admission during bed rest and, being unrelated to the mobilisation programme, are not considered further. The 10 deaths that occurred within 24 weeks in the 127 patients mobilised are analysed below.

Deaths within 6 weeks after mobilisation (Table 3)

Three patients died within 6 weeks and each had had 5 to 10 days initial bed rest. Two had prolonged cardiac failure from the time of admission until death, indicating severe infarction. Neither had evidence of cardiac rupture at necropsy. A third was well until sudden death at home in the 5th week. None of the 74 mobilised after 2 to 4 days' bed rest died within 6 weeks. It is clear that too rapid mobilisation did not lead to an excess of deaths in the early postinfarction period.

Deaths from 6 to 24 weeks after mobilisation (Table 3)

Seven patients died within 6 to 24 weeks. Three had been mobilised slowly after more than 10 days' bed rest on account of severe infarction and early complications. Each had persistent cardiac failure until death, and one had pulmonary embolism.

The other 4 patients had been mobilised rapidly after 2 to 4 days' bed rest. One had ventricular fibrillation, in the 7th week, 2 died suddenly at home in the 10th and 12th weeks, and 1 died of recurrent infarction and cardiac failure in the 15th week. It is

Table 3 *Mortality within 24 weeks in 127 patients mobilised*

Rapidity of mobilisation		*Deaths within 6 wk*	*Deaths from 6 to 24 wk*
No. of patients	*Days bed rest*		
74	2–4	—	4
42	5–10	3	—
11	> 10	—	3

unlikely that these 7 deaths, occurring so long after infarction, were related to early mobilisation.

NON-FATAL CARDIAC COMPLICATIONS

Non-fatal cardiac complications within 6 weeks after mobilisation (Table 4)

Eight (6·5%) of the 127 mobilised had 9 non-fatal cardiac complications within 6 weeks. (One patient had recurrent myocardial infarction in hospital and was later readmitted with cardiac pain.)

Non-fatal cardiac complications from 6 to 24 weeks after mobilisation (Table 5)

Six (5%) of the 127 mobilised had 8 non-fatal cardiac complications from 6 to 24 weeks. (One patient was admitted 3 times with cardiac pain.) Some patients had more than one non-fatal cardiac complication and some patients who died had previously had non-fatal cardiac complications. After 6 weeks in the 127 mobilised, 116 (91%) were uncomplicated, and after 24 weeks, 105 (88%) were uncomplicated.

READMISSIONS

Altogether 12 patients were readmitted on 17 occasions within 24 weeks. Seven were readmitted within 6 weeks, but only one within 4 weeks. Thus early discharge did not result in early readmission.

THROMBOEMBOLIC DISEASE

Thromboembolic disease was diagnosed clinically and, where indicated, by chest *x-ray* and lung scanning. Each of the 7 patients with pulmonary infarction had more than 8 days' bed rest. In these 7 patients, 4 developed pulmonary infarction during bed rest after the fourth day, and one later in hospital after mobilisation. The other 2 were readmitted because of pulmonary infarction and one patient died shortly after readmission.

A deep venous thrombosis was diagnosed clinically during bed rest in one patient who had pulmonary embolism.

Although thromboembolic disease occurred in patients who had prolonged bed rest of more than 8 days, these were patients who had severe infarction.

Table 4 *Nonfatal cardiac complications within 6 weeks in 127 patients mobilised*

Complication	*Days of bed rest*		
	2–4 days (74 patients)	*5–10 days (42 patients)*	*10 days (11 patients)*
Reinfarction definite	2	—	—
suspected	3	—	1
Cardiac failure	1	—	—
Ventricular fibrillation	—	1	—
Atrial fibrillation	—	1	—

Table 5 *Nonfatal cardiac complication from 6 to 24 weeks in 127 patients mobilised*

Complication	*Days of bed rest*		
	2–4 days (74 patients)	*5–10 days (42 patients)*	*10 days (11 patients)*
Reinfarction definite	2	1	1
suspected	1	2	—
Cardiac failure	—	1	—

VENTRICULAR ANEURYSM

All patients were repeatedly examined by praecordial palpation. Cardiac screening was undertaken when ventricular aneurysm was suspected for any reason, but none was found.

CARDIAC NEUROSIS

Formal psychological testing was not undertaken. One patient developed depression and was transferred to a psychiatric hospital and another became depressed after 24 weeks. Overt cardiac neurosis was notably absent.

Discussion

EARLY MOBILISATION AND DISCHARGE

Mobilisation after uncomplicated myocardial infarction has been shown to be as safe after 2 days as after 9 days of bed rest (Hayes *et al.*, 1974). Our study supports the safety of rapid mobilisation within a few days in uncomplicated cases. In the 74 patients mobilised after only 2 to 4 days in uncomplicated infarction or only transient complications, there were no deaths in 6 weeks and 4 (5%) in 24 weeks. In a group of similarly uncomplicated patients mobilised after either 7 or 21 days' bed rest, Harpur *et al.* (1971) found mortality rates of 5 and 8 per cent, respectively, which were not statistically significantly different. Though strict comparison between different studies is not possible, we have no reason to suspect that a period of bed rest longer than 2 to 4 days is safer. It is, therefore, unnecessary.

There are fewer reports of mobilisation after complicated myocardial infarction. A recent controlled trial provided some evidence that mobilisation was not only safe, but safer after 6 to 8 days' bed rest, compared with 13 to 15 days' bed rest (Abraham *et al.*, 1975). In our group there was a higher complication rate in the 53 patients mobilised after more than 4 days. In particular, there were 3 deaths in the 11 patients mobilised after 10 days out of a total of

10 deaths in the 127 patients mobilised. However, the patients mobilised more slowly had more severe or prolonged complications.

An ideal trial should compare matched groups of patients with similar severity of infarction and similar complications undergoing several widely varying schedules. This would require large numbers and could not be done from a single centre. At the present time, without firm evidence about mobilisation after complicated myocardial infarction, commonsense dictates that any schedule should be flexible according to individual needs. We found that mobilisation was delayed beyond the fourth day in 42 per cent of survivors but only 9 per cent for longer than 10 days.

Datey *et al.* (1973) in Bombay, using selection criteria for ambulation which included absence of angina, cardiomegaly (*x*-ray), ST shift of 2 mm or more on the electrocardiogram, abnormal blood pressure (systolic <90 mmHg, diastolic >100 mmHg or significant orthostatic fall in mean pressure >7 mmHg) or a resting heart rate >100/min, allowed only 25 per cent of survivors of myocardial infarction to walk 30 yards in 2 weeks. These criteria seem excessively strict and very likely to induce introspection and cardiac neurosis.

Advantages of early mobilisation are a shorter hospital stay for the patient and more economical use of hospital beds. In this series, 69 per cent were discharged within 14 days.

Adgey (1969), in a group of patients spending less than 18 days in hospital after infarction, had no deaths or readmissions within 2 weeks of discharge. It was concluded that early discharge did not lead to early readmission or death from complications requiring resuscitation facilities. Similarly, we had only one readmission within 2 weeks of discharge and the earliest outpatient death occurred in the 5th week after infarction. It could be argued that a prolonged hospital stay of 6 weeks would sometimes give a chance of resuscitation, but the results of late cardiac arrest are not good (Thompson and Sloman, 1971).

REHABILITATION AND SECONDARY PREVENTION

It is unusual for British physicians to undertake more than a single review of patients discharged after myocardial infarction. We found that a period of convalescence with a graded exercise programme allayed anxiety and led to a more confident return home. Exercise was not medically supervised or monitored and there were no deaths during this period. A clearly explained regimen of graded exercises at home might serve equally well.

An intensive programme of secondary prevention was started after discharge from hospital. This also provided an opportunity for giving advice on aspects of rehabilitation other than secondary prevention, such as driving, sexual intercourse, and return to work. Patients were taught how to improve their own health and it was explained how a coronary attack could be the beginning of a more healthy way of life.

Return to work is the best form of rehabilitation. Nagle *et al.* (1971) found that only 50 per cent of a group of Birmingham car workers had returned to work within 16 weeks of myocardial infarction, in comparison with Royston (1972) who encouraged 90 per cent of patients back to work within 3 months with a policy of explanation and reassurance in hospital and at a review clinic. We agree that unequivocal advice can lead to a high rate of early return to work and found that 70 per cent had returned within 16 weeks and 79 per cent within 24 weeks.

Wishnie *et al.* (1971) found in a small group recovering from myocardial infarction that most felt anxious or depressed in the month after discharge, and about 30 per cent of these patients wished to return to hospital in the first week. Few had had advice about physical exercise and most were frustrated by inactivity. Wynn (1967) found that anxiety and depression accounted for disability in about 25 per cent of patients who remained unemployed after myocardial infarction. We did not undertake formal psychological assessment but were impressed by the lack of pyschiatric disturbance. We consider that cardiac neurosis can be avoided by clear explanation and a positive approach to rehabilitation.

At one time it was thought that early mobilisation might lead to ventricular aneurysm formation (Moyer *et al.*, 1951). Our findings are in agreement with Harpur *et al.* (1971) who showed no difference in the incidence in patients mobilised after either 8 or 21 days and Groden *et al.* (1967) after 15 or 25 days.

It has been thought that bed rest predisposes to thromboembolism but Hayes *et al.* (1974) found no difference in the incidence of deep venous thrombosis detected by radioactive iodine labelled fibrinogen in patients mobilised rapidly after 2 days, or more slowly after 9 days. We have no evidence to show that rapid mobilisation reduced the incidence of thromboembolism because most of our patients also received anticoagulants. However, it is noteworthy that none of the uncomplicated patients who were mobilised after 2 to 4 days had clinical evidence of thromboembolism.

In 1972, Rose stated that the conservative physician who wishes to restrict his patients' recovery needs to prove his case. Our experience confirms the safety of rapid mobilisation and we consider that this practice should lead to early discharge, facilitate rehabilitation, and be the first stage in secondary prevention.

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Transmural myocardial infarction in young women taking oral contraceptives

Evidence of reduced regional coronary flow in spite of normal coronary arteries

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A normal coronary arteriogram after transmural myocardial infarction is a well-recognised phenomenon, but the pathophysiology remains unclear in most cases. A possible aetiological role of oral contraceptives is suggested by the occurrence of unequivocal myocardial infarction with normal or near normal coronary arteries in 4 young women who had been taking oral contraceptives. While the cause-effect relation of coronary thrombosis and myocardial infarction remains controversial in patients with coronary atherosclerosis, a primary occlusion of macroscopically normal coronary arteries by cellular elements of blood appears possible in these cases. The action of contraceptives, then, would be analogous to their thrombogenic effect in peripheral veins and cerebral arteries.

Absence of atherosclerotic lesions in these patients favours spontaneous thrombolysis and restoration of normal vessel patency in many of these cases. Myocardial blood flow in the region of the damaged left ventricular wall remains low in spite of normal coronary arteries. Reduced perfusion in infarcted areas is assumed to be the consequence of structural and functional alterations at precapillary and capillary level rather than an effect of obstructive coronary disease.

Myocardial infarction in patients with normal coronary arteries is reported with increasing frequency. Though this syndrome is still poorly understood, it seems today from clinical, angiographic, and postmortem evidence that myocardial infarction in young women taking oral contraceptives may represent a specific subgroup of this disease. The following presentation of 4 additional cases will attempt to analyse the pathophysiology of this subgroup and discuss the pathogenic role of contraceptives in myocardial infarction. Special emphasis will be put on regional myocardial blood flow in the area of infarction supplied by angiographically normal coronary arteries because so little is known about this subject (Lichtlen *et al.*, 1976). Moreover, the study of regional myocardial blood flow in these patients might lead to some conclusions with regard to the pathophysiology of this specific syndrome and of coronary heart disease in general.

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Methods

Coronary and left ventricular angiocardiography were performed by the Sones or Judkins techniques. In each case the angiograms were carefully analysed for coronary lesions using multiple LAO and RAO-projections. Left ventriculograms were performed in 45 degree RAO-projections.

In 3 of the 4 patients, regional myocardial perfusion was analysed both by (1) the Xenon residue detection technique (Ross *et al.*, 1964; Dwyer *et al.*, 1973; Hundeshagen *et al.*, 1976); and (2) by microsphere perfusion scintigraphy (Ashburn *et al.*, 1971).

XENON RESIDUE DETECTION

The praecordial Xenon clearance technique was performed by use of a Pho-Gamma-3 Nuclear Chicago scintillation camera in conjunction with a CDC 1700 computer. After intracoronary injection of 10 mCi ^{133}Xenon, the initial Xenon distribution

(ID-Xe) recorded during 10 seconds after peak activity and regional Xenon clearance for each of 4096 matrix points of the gamma camera were assessed. Thus, Xenon data were analysed both for flow distribution (ID-Xe) analogous to microsphere scintigraphy and as myocardial blood flow (MBF-Xe, ml/min per 100 g) derived from tracer washout. Assessment of myocardial blood flow was performed by analysis of the initial monoexponential washout slope by means of the Kety-Schmidt formula (Kety and Schmidt, 1945). Discrimination of extracardiac activity was achieved by fluoroscopically positioned external markers delineating the borders of the heart and by statistical means based on rejection of all matrix points that either reached their peak later than 15 seconds after Xenon injections or recorded less than 15 per cent of maximal isotope activity.

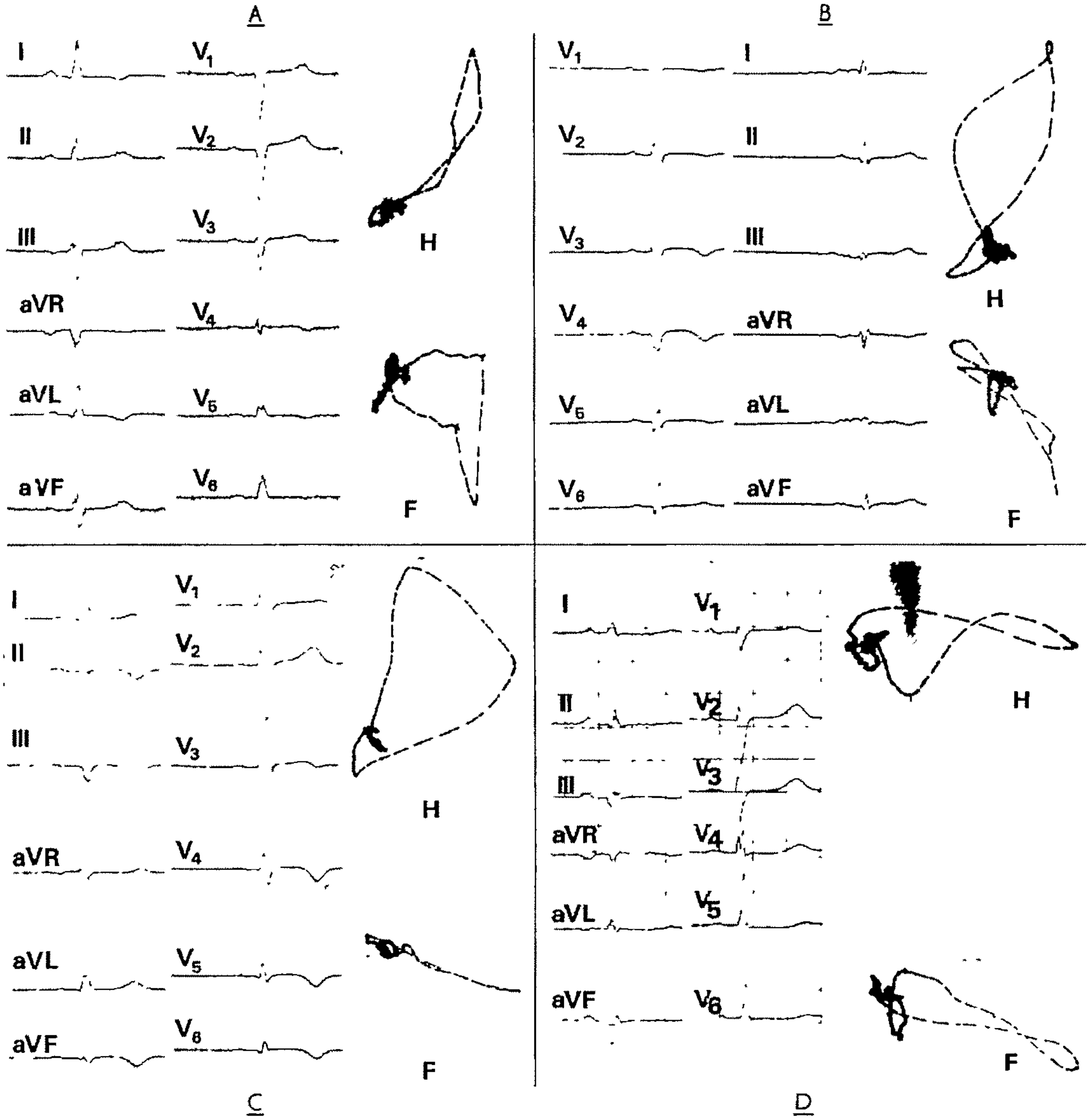


Fig. 1 *Electrocardiograms and vectorcardiograms of the 4 patients.*

MICROSPHERE PERFUSION SCINTIGRAPHY

Myocardial perfusion scintigraphy was performed with ^{99m}Tc-labelled human albumin microspheres (MPS-Tc). Regional activity was recorded both with the gamma camera and with a rectilinear scanner in conjunction with a core memory.

Case reports

The four women had been referred for diagnostic coronary arteriography and selection for surgery.

CASE 1 (C.S.)

A 33-year-old mother of two children. No family history of premature atherosclerosis. The risk factors included history of smoking 1 to 2 packets of cigarettes daily over 13 years. Oral contraceptives (Lyndiol=2·5 mg lynoestronol + 0·075 mg mestranol) over the past 7 years. In March 1975 acute myocardial infarction without premonitory signs of angina pectoris. After the infarct there was no chest pain but complaints of dyspnoea and palpitation on exertion. Physical examination was normal. Blood pressure, serum cholesterol, triglycerides, and glucose were all within normal limits. Electrocardiogram and vectorcardiogram were consistent with old anterior myocardial infarction (Fig. 1A). Cardiac catheterisation with coronary and left ventricular angiocardiography eight months after the acute event showed left ventricular end-diastolic pressure at rest to be raised at 15 mmHg (Table); akinesis of the apical two-thirds of the anterior wall with paradoxical motion of the apex, and normal coronary arteries (Fig. 2).

CASE 2 (I.K.)

A 40-year-old woman, previously in good health. The family history was negative for premature atherosclerosis. Risk factors included cigarette smoking (1 packet per day) over 16 years. Oral contraceptives had been taken for 18 months but were stopped one year before the infarction; from this time up to the infarction, monthly intramuscular injections of oestrogen (12 mg diethylstilboestrol) had been given; during the 12 days immediately preceding the infarction an additional oral oestrogen-progestogen combination (Primosiston= 2 mg norethisteroneacetate +0·01 mg ethinyloestradiol) had been administered. In March 1974, a sudden crushing chest pain led to hospital admission for acute myocardial infarction. Ten hours after the first symptoms, streptokinase (1 750 000 units) was infused over 16 hours. Eight months after the event she was referred for further evaluation because of intermittent burning retrosternal pain on strenuous exercise. Blood pressure, serum cholesterol, triglycerides, and glucose were all within normal limits at the time of the study. The electrocardiogram and vectorcardiogram showed anterolateral myocardial infarction (Fig. 1B). Cardiac catheterisation (Table) indicated normal resting haemodynamics; angiocardiography showed akinesis of the apical half of the anterior and apical third of the diaphragmatic wall of the left ventricle, and normal coronary arteries (Fig. 2).

Myocardial perfusion scintigraphy showed a large defect of activity corresponding to the akinetic left ventricular area (Fig. 3). The functional image of regional blood flow and the printout of flow rates showed the highest flow in the distribution of the left circumflex branch and in parts of the interventricular septum, whereas flow values were low in the inferior septum, the apex and the lower part of the anterior free wall of the left ventricle. Xenon washout was normal in a portion of the interventricular septum indicating that parts of this structure (probably supplied by the first septal branch) were perfused normally. Since perfusion scintigraphy (MPS-Tc) showed little activity in the septal area, the total mass of well-perfused interventricular myocardium may be presumed to be small. It seems probable that the obstruction in this case was located below the first septal branch; this would also be in agreement with the left ventriculogram showing an akinetic area below the papillary muscle, contractions in the middle and upper parts of the anterior wall still being normal (Fig. 2).

CASE 3 (R.C.)

A 34-year-old mother of one child. Family history negative for premature atherosclerosis. No history of smoking. Oral contraceptives (Eugynon=0·5 mg dl-norgestrel +0·05 mg ethinyloestradiol) had been taken for 13 years with only brief interruptions. She had a minor attack of chest pain five months before the event. In March 1975 she was admitted to hospital because of sudden severe retrosternal pain associated with nausea and vomiting; electrocardiogram and serum enzymes were diagnostic of acute inferolateral infarction. The course was uneventful. Blood pressure, serum cholesterol, triglycerides, and glucose were all within normal limits. Electrocardiogram and vectorcardiogram (Fig. 1C) indicated an inferior infarction, not recent. Cardiac catheterisation 5 weeks after the event showed normal haemodynamics (Table). Left ventriculogram showed hypokinesis of the diaphragmatic portion of the apex; the coronary arteries were normal (Fig. 2).

Microsphere scintigraphy and initial Xenon distribution revealed a perfusion deficit in the inferolateral region of the left ventricle. Xenon washout was found to be homogeneous (Table).

Table

Case No.	*Angiocardiography*		*Systolic half axial shortening (%)*						*Haemodynamics*			*Myocardial perfusion: regional reduction of*	
			Anterior			*Inferior*							
	Coronary artery	*Left ventricle*	*Basal*	*Medial*	*Apical*	*Basal*	*Medial*	*Apical*	*LVEDP*	*Cardiac index (mmHg)*	*Stroke work index (g m/m² BSA)*	*MBF-XE*	*MPS-TC*
1	N	Akinesis of anterior wall	*13*	*+4*	*+12*	58	70	43	15	3 5	57	—	—
2	N	Akinesis of anterior wall	39	*9*	*8*	51	90	*+25*	11	3·6	63	−65% $\left(\frac{53}{152}\right)$	−65%
3	N	Hypokinesis of inferolateral wall	51	38	27	49	52	*10*	10	4·2	67	−7% $\left(\frac{106}{114}\right)$	−55%
4	25% left circumflex branch	Akinesis of inferolateral wall	37	23	55	*+4*	*0*	*9*	10	4 0	59	−41% $\left(\frac{61}{104}\right)$	−45%

LVEDP, left ventricular end-diastolic pressure; regional reduction of MBF-Xe, per cent reduction of blood flow in damaged LV area as compared with normal LV area; in parenthesis blood flow in ml/min per 100 g damaged LV area over flow in normal area. Reduction of MPS-Tc, regional scintigraphic activity in damaged LV area in per cent of normal area. Abnormal systolic half axial shortening indicated by italic type.

CASE 4 (U.D.)

A 37-year-old mother of two children. Family history negative for premature atherosclerosis. No smoking history. Oral contraceptives (Ovanon= 7 × 0·08 mg mestranol and 15 × 0·075 mg mestranol ±2·5 mg lynoestrenol) had been taken for 12 years. No symptoms were referrable to the cardiovascular system before an acute myocardial infarction in August 1974. At the time of cardiac catheterisation 16 months later, blood pressure, serum triglycerides, and glucose were normal, serum cholesterol was moderately raised at 7·7 mmol/l (normal: less than 6·5 mmol/l). Electrocardiogram and vectorcardiogram showed old inferior myocardial infarction (Fig. 1D). Ventriculography indicated extensive akinetic area in the diaphragmatic wall of the left ventricle. Coronary arteriography was normal with the exception of an isolated focal mild stenotic lesion of less than 30 per cent luminal diameter in the mid portion of the dominant left circumflex coronary artery (Fig. 2). Perfusion scintigraphy and Xenon clearance demonstrated clearly diminished blood flow to the akinetic inferolateral portion of the left ventricle (Table).

Discussion

Several reports during the past few years have indicated that the use of oral contraceptives results in an 8- to 10-fold increase in the risk of venous thrombosis and pulmonary emboli as compared with subjects not taking oral contraceptives (Vessey and Doll, 1969). The risk of arterial thrombosis leading to ischaemic cerebrovascular events appears to be increased as well (Masi and Dugdale, 1970). Furthermore, occurrence of myocardial infarction is reported with increasing frequency, and a statistically significant correlation between the mortality and morbidity of myocardial infarction in young women and the use of oral contraceptives has been shown by extensive epidemiological studies (Mann *et al.*, 1975). Nevertheless the number of well-documented cases is small, and precise information on the status of the coronary vessels and on concomitant atherogenic risk factors is available in only a few of these communications. To our knowledge this is the first study analysing regional myocardial perfusion in such patients.

(a) MYOCARDIAL PERFUSION

Regional myocardial perfusion was studied in 3 patients (Table). In spite of angiographically normal or almost normal coronary arteries, microsphere scintigrams (MPS-Tc) and initial Xenon distribution (ID-Xe) showed abnormal flow distribution in all 3 patients (Table). Reduced Xenon washout (MBF-Xe), however, was found only in the 2 patients with regional akinesis (cases 2 and 4) whereas regional Xenon clearance was normally homogeneous in the patient with inferolateral hypokinesis (case 3). This is thought to result mainly from the fact that analysis of the initial monoexponential slope of Xenon washout curves yields results that are weighted in favour of well-perfused areas within each solid angle and thus probably refers to remaining areas of viable myocardium rather than to scar tissue in hypokinetic areas. Moreover, adequate projection of the inferior left ventricular wall is difficult to achieve, since overlying normal anterior left ventricular wall areas tend to produce normal tracer washout curves.

In view of the unobstructed coronary arteries, one has to assume that the reduction of flow and perfusion observed in these patients is attributable either to reduced tissue oxygen demand or to structural changes at the precapillary or capillary level. Thus, reduced perfusion and flow rates in patients with myocardial infarction and severe coronary obstruction (Dwyer *et al.*, 1973; Engel *et al.*, 1976a) are concluded to be the result not only of the impediment of flow induced by obstructions of the large extramural coronary arteries; they probably also reflect alterations at the cellular level which increase resistance to flow after myocardial infarction.

(b) MECHANISM OF MYOCARDIAL INFARCTION DURING ORAL CONTRACEPTIVE MEDICATION

The localised perfusion deficit in spite of normal

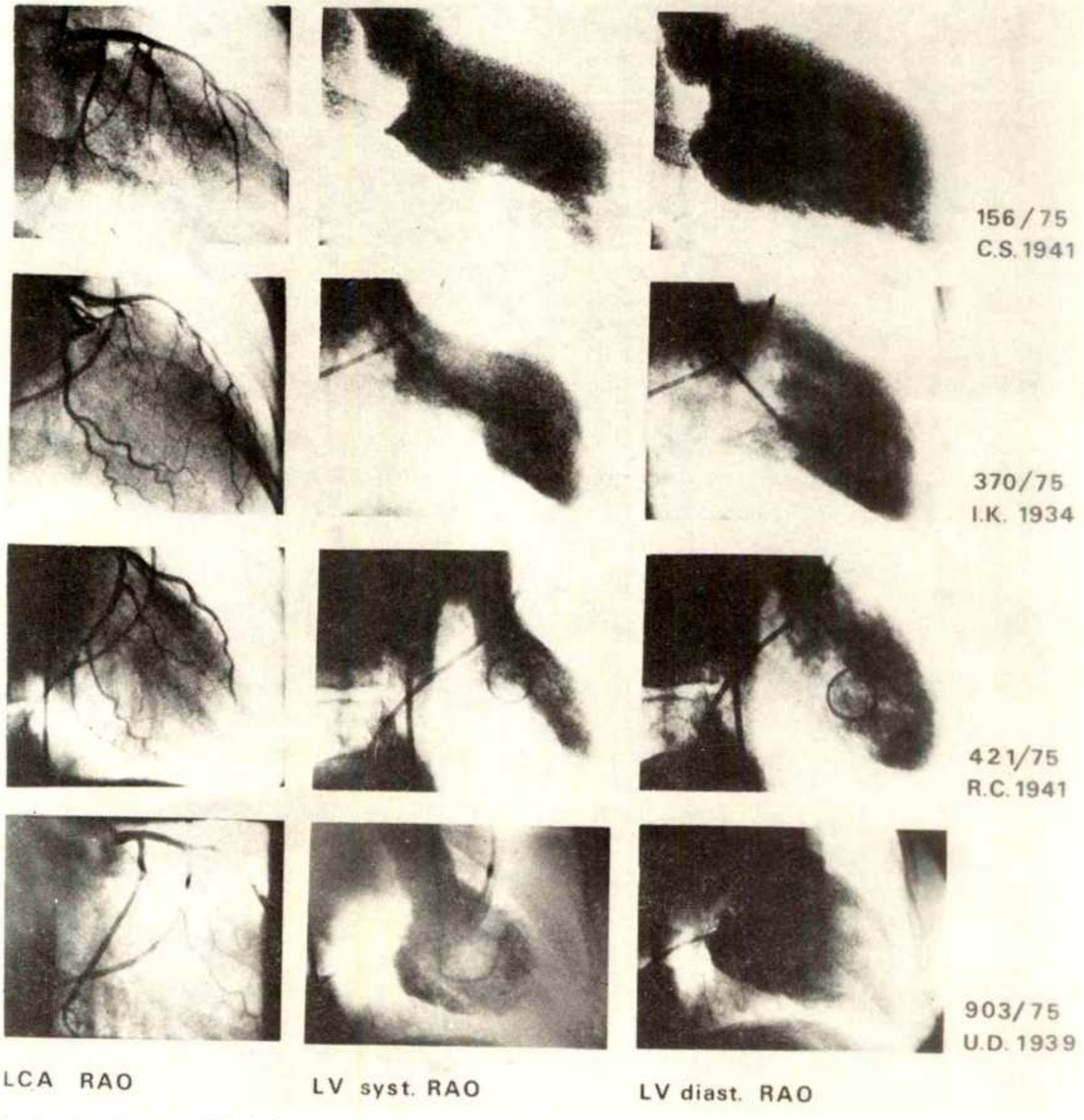
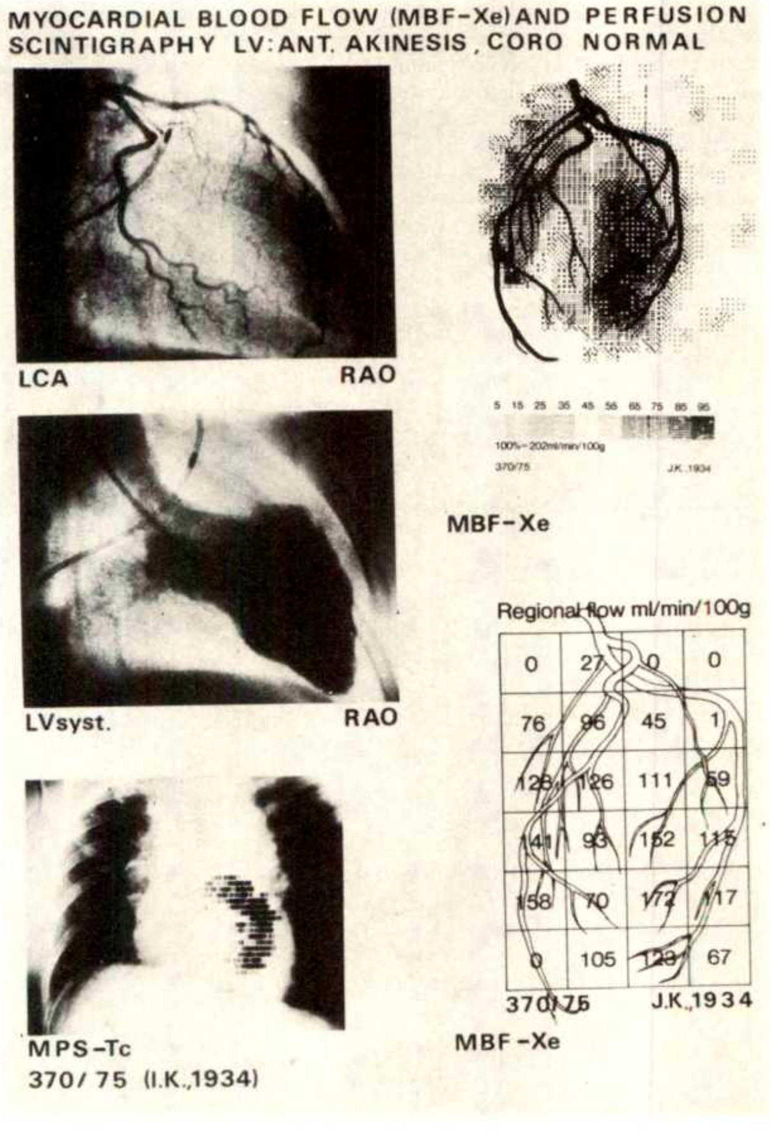


Fig. 2 *Arteriograms of the left coronary artery (LCA) and left ventriculograms in right anterior oblique (RAO) projections.*



0	27	0	0
76	96	45	1
128	126	111	59
141	93	152	115
158	70	172	117
0	105	129	67

Fig. 3 *Myocardial blood flow (MBF-Xe) and microsphere perfusion scintigram (MPS-Tc) in case 2 with anterior wall akinesis and normal coronary arteries. Top left frame, left coronary artery. Middle left frame, systolic phase of left ventriculogram. Bottom left frame, perfusion scintigram with superimposed chest x-ray film. Right frames, myocardial blood flow displayed as functional image (top) and numerically in ml/min per 100 g (bottom) with superimposed correctly aligned coronary arteriogram (LAO projections).*

coronary vessels indicates myocardial damage, and the history as well as electrocardiographic and ventriculographic findings are diagnostic of myocardial infarction in each of our patients. Causes for transmural myocardial infarction in the absence of coronary atherosclerosis include coronary artery spasm, small vessel disease, and thromboembolic phenomena with spontaneous restitution of vessel patency.

The role of coronary artery spasm in the production of myocardial infarction has been discussed repeatedly (Carleton and Johnson, 1974), but myocardial infarction related to coronary spasm has been reported only subsequent to local arterial stimulation by catheter (Cheng *et al.*, 1972; Engel *et al.*, 1976b). The assumption of 'small vessel disease' is difficult to accept as the primary cause of transmural myocardial infarction.

In our opinion the most plausible hypothesis explaining myocardial infarction in young women taking oral contraceptives is thromboembolic mechanism. The way in which oral contraceptives might produce thrombotic coronary occlusions is hypothetical, but is analogous to their thrombogenic effect in peripheral and hepatic veins and in cerebral arteries. Oestrogens are known to enhance coagulability by increasing platelet adhesiveness and by augmenting the activity of clotting factors VII and X (Dugdale and Masi, 1969). In addition, microscopical changes of the arterial wall that might be related to thrombus formation have occurred after oestrogen medication (Irey *et al.*, 1970).

A review of communications on possible oestrogen-related myocardial infarction based on angiographic results (Dear and Jones, 1971; Glancy *et al.*, 1971; Waxler *et al.*, 1971; Kimbiris *et al.*, 1972; Henderson *et al.*, 1973; Maleki and Lange, 1973; Ciraulo, 1975) or necropsies (Hartveit, 1965; Naysmith, 1965; Osborn, 1965; Dalgard and Gregersen, 1969; Stout, 1969; Weiss, 1972) tends to corroborate this assumption because these reports document a higher than average incidence of coronary thrombosis and little evidence of generalised atherosclerosis. In contrast, diffuse and widespread atherosclerotic coronary disease is the common finding after myocardial infarction of atherosclerotic aetiology (Roberts and Buja, 1972). The observations presented here are not sufficient to decide whether myocardial infarction that might be related to contraceptive medication is a discrete disease entity unrelated to coronary atherosclerosis or common atherogenic risk factors. This hypothesis does not agree with observations by Oliver (1970) and Radford and Oliver (1973) who report that the risk of taking oral contraceptives is increased most in women with atherogenic risk factors.

The finding of normal or almost normal coronary arteries in our patients is not inconsistent with thromboembolic occlusions. Spontaneous resolution of occlusive coronary clots has been shown experimentally by Weisse *et al.* (1969). In man complete resolution of thrombotic material accidentally embolised into the coronary arteries during cardiac catheterisation has been documented repeatedly (Agarwal *et al.*, 1975). Absence of atherosclerotic lesions that are known to inhibit thrombolysis is felt to enhance restoration of vessel patency under these circumstances (Weisse *et al.*, 1969).

In conclusion a rare aetiological relation between the use of oral contraceptives and myocardial infarction appears possible in susceptible women. The relation between myocardial infarction related to contraceptive pills and coronary atherosclerosis remains undefined. As the regional myocardial flow studies indicate, perfusion of previously infarcted left ventricular wall areas is reduced even after complete restoration of vessel patency.

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Evaluation of evolution of myocardial infarction by serial determinations of serum creatine kinase activity

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In order to investigate the relation between the release of creatine kinase (CK) in acute myocardial infarction and the evolution of infarction, the appearance functions of CK (release of CK from the heart into the circulation) were calculated by the modified method of Sobel and associates from the serial determinations of serum CK activity in 50 patients with acute myocardial infarction. The relation of the time between the onset of infarction and the peak value of the appearance function to the duration of the evolution of abnormal Q waves in 14 patients with inferior infarction and to the duration of pain in all patients was investigated.

The duration of CK release from the heart averaged 37·2±2·4 hours and correlated well with the total CK released ($r=0{\cdot}665$) which represents the infarct size. The mean per cent of the total CK eventually released by the time of maximum ΣQ (sum of the amplitude of Q wave in leads II, III, and aVF) was 80·0±6·4 per cent and that of CK released while pain persisted was 72·0±3·9 per cent. These results strongly suggest that the appearance function of CK reflects the evolution of myocardial infarction.

In myocardial infarction the incidence of cardiogenic shock and heart failure is related to the extent of myocardial damage (Harnarayan *et al.*, 1970), and various treatments which improve the balance of oxygen supply in relation to the demand of the ischaemic myocardium are used to try to limit the injury to the myocardium (Maroko *et al.*, 1972a, b; Pelides *et al.*, 1972). Thus, it is important to assess the time course of the evolution of myocardial infarction as well as the ultimate infarct size, in order to decide upon the effectiveness of such treatments.

Recently a method for assessing the infarct size from serial determinations of serum creatine kinase (CK) activity was reported by Sobel and associates (1972). Though the 'appearance function' of myocardial CK (the rate of release of CK from the infarcted myocardium into the circulation) can be calculated by this method and should indicate the evolution of myocardial infarction as a function of time (Norris *et al.*, 1975; Witteveen *et al.*, 1975), its clinical significance has not been extensively studied (Mathey *et al.*, 1975). The present study, in patients with acute myocardial infarction, was undertaken to investigate the relation of this 'appearance function' to the duration of chest pain. We wanted to evaluate this function as a clinical guide in assessing the evolution of myocardial infarction.

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Subjects and methods

Fifty patients with acute myocardial infarction were included in this study. They were between the ages of 43 and 78 years (average 60·2) and were admitted to the Coronary Care Unit of Sakurabashi Watanabe Hospital within 12 hours after the onset of chest pain and survived for more than 4 days. Patients with reinfarction within a few days after the onset, those who were given morphine, or those whose onset was not clear were not included. Twenty-three patients had anterior infarction (including septal and lateral infarction) and 27 patients had inferior infarction (including pure posterior and inferolateral infarction). From past history and electrocardiograms before this admission, 16 patients were judged to have had previous myocardial infarction. Patients were divided into two groups: group A included 30 patients without heart failure and group B included 20 patients with heart failure.

SERUM ENZYME DETERMINATIONS

Samples of peripheral venous blood were obtained from the patients every 4 hours during the first 24 hours after admission and thereafter every 6 hours until serum CK activity returned to normal. The sample was allowed to clot at room temperature, the serum was separated, and stored immediately at 4°C. The determinations were made within 15 hours after sampling. As intramuscular injections can cause a release of CK (Meltzer *et al.*, 1970), all injections were given either intravenously or subcutaneously.

MATHEMATICAL ANALYSIS OF DATA

The appearance function of CK released from the infarcted myocardium was calculated according to the method of Sobel *et al.* (1972), modified by Norris *et al.* (1975). The principle underlying the calculation is that the instantaneous rate change of serum CK activity (dE(t)/dt) is determined by the release rate of myocardial CK from the heart (f(t)) and its disappearance rate from the serum (k). Thus:

$$dE(t)/dt = f(t) - kE(t)$$

Where E(t) represents the instantaneous serum CK activity subtracting the individual basal value. By this formula, the appearance function (f(t)) of CK released from the infarcted myocardium is calculated as follows:

$$f(t) = dE(t)/dt + kE(t).$$

Accordingly total CK released can be calculated by integrating the appearance function as follows:

$$\int_0^t f(t)dt = E(t) + \int_0^t kE(t).$$

DURATION OF PAIN

Patients' complaints of chest pain were recorded at least four times a day by investigators who did not know the enzyme values. In this study, we included as cardiac pain not only typical chest pain but also any oppressive feeling in the chest, back pain, and, in inferior infarction, epigastric pain, but we excluded low back pain which could have been the result of continued bed rest. In our series, only the duration of pain was studied. The severity of pain, which involves a subjective assessment, was not investigated. In no patient was the pain completely relieved after the administration of analgesic agents, though its severity was effectively reduced.

EVOLUTION OF ABNORMAL Q WAVES IN ELECTROCARDIOGRAMS

Standard 12-lead electrocardiograms were recorded at least three times a day for the first several days and once daily thereafter. In 14 of the 27 patients with inferior infarction, the amplitudes of newly developed Q waves in leads II, III, and aVF were measured serially. Thirteen patients were excluded as follows:

(1) Patients with bundle-branch block in the electrocardiogram.
(2) Patients with previous inferior infarction.
(3) Patients with significant changes of the electrical axis.

In patients with bundle-branch block or those with previous inferior infarction, determination of the amplitudes of the new Q waves in leads II, III, and aVF proved difficult. Patients with anterior infarction were also excluded from the electrocardiographic analysis since in almost all such cases quantitative measurements were impossible in praecordial leads because the new Q waves were masked by the QS complex.

As an index of evolution of infarction (ΣQ), we obtained the sum of the amplitudes of Q waves in leads II, III, and aVF divided by the sum of the amplitudes R_{I}, S_{aVR}, and R_{aVL} to correct for transient low voltage. Though the duration of the Q wave is believed to be more valuable than its amplitude in the evaluation of a transmural infarction, we measured serial changes of the amplitude of Q waves as ΣQ, since the measurement of their duration in a standard record (paper speed of 2·5 cm/s) was very difficult.

Individual appearance functions of released CK were calculated from the serial changes of serum CK activity for each of the 50 patients, and the relation of this function to the duration of pain, as well as to the evolution of abnormal Q waves in electrocardiograms was studied.

Results

(1) APPEARANCE FUNCTION OF RELEASE OF CK (f(t))

The appearance functions calculated by the modified method of Sobel *et al.* in 4 representative cases are illustrated in Fig. 1a to 1d. In case 6 (Fig. 1a), the release rate of CK (shown by the solid line f(t)) increased rapidly to a peak 9 hours after the onset and decreased gradually to zero 36 hours after the onset, while the serum CK activity (dotted line E(t)) showed a peak value at 24 hours and fell to normal 72 hours after the onset. This shows that the release of CK from the heart into the circulation ceased long before the serum CK activity returned to normal.

Fig. 1b shows another case representative of early reinfarction which was excluded from the 50 patients of this study. The appearance function of this patient clearly shows the second attack of infarction after the conclusion of evolution of the first attack. This, however, could not have been clearly

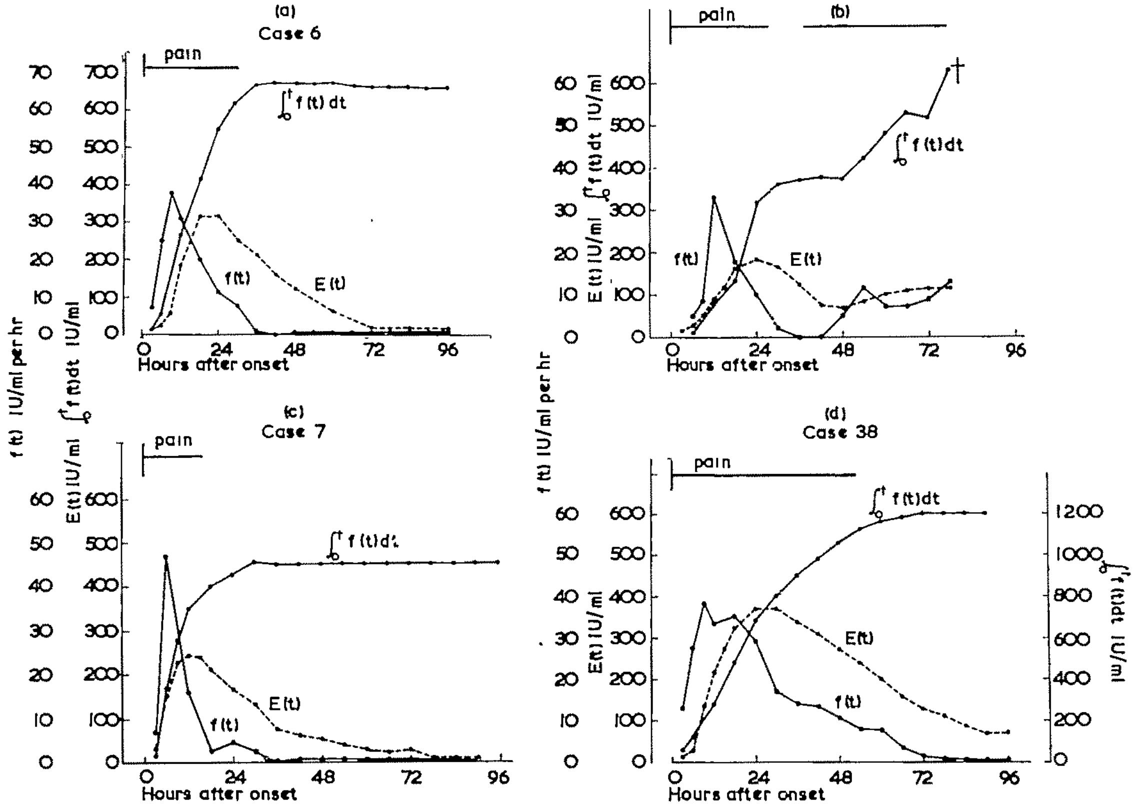

Fig. 1 *Serial serum CK activities (E(t), subtracting individual basal value), the appearance function of CK (f(t)), and the cumulated CK released* ($\int_0^t f(t)dt$) *in 4 representative cases.*

shown by the serum CK activity alone, since it never returned to a normal level. Electrocardiograms of this patient confirmed the anterior infarction corresponding to the second rise of the appearance function. Fig. 1c illustrates a case whose appearance function indicates that the major release of CK was completed within 18 hours, while Fig. 1d shows a case whose release rate of CK decreased much more slowly.

The duration of the release of CK in the 50 patients ranged from 12 to 87 hours, averaging 37·2 ±2·4 (mean ±SE) hours (see Table 1), and Fig. 2 shows the relatively high correlation ($r = 0{\cdot}665$) between the duration of release of CK and total CK released ($\int_0^t f(t)dt$). This indicates that infarct size determines not only the total CK released as has been established, but also the duration of its release.

The mean peak time of the release of CK was 12·4 ±0·9 hours from the onset. In fact in 22 of 50 patients, the release rate reached a peak within 10 hours. An average of 62·2 per cent of total CK released appeared in the circulation in the first half of the duration of release, which indicates that the major part of the evolution of infarction occurred in that time.

The mean duration of CK release in 30 patients without heart failure (group A) was significantly shorter than that in 20 patients with heart failure (group B) ($P < 0{\cdot}01$, see Table 1). There was, however, no significant difference in the ratio of CK released by the time of peak release rate to total CK released, between groups A and B. However, the mean ratio of CK released within the first 24 hours after the onset to the total CK released of group A (87·1 ±2·6%) was significantly greater than that of group B (71·4 ±4·3%). Since group B (with heart failure) includes the cases with the clinically more severe involvement, it is reasonable to conclude that the longer duration of CK release in this group is the result of larger infarct size. This is further confirmed by the finding that the mean total CK released in group B was significantly greater than in group A ($P < 0{\cdot}005$, see Table 2).

Table 1 *CK release and duration of pain*

	No. of subjects	*Duration of release of CK (h)*	*Total CK released ($\int_0^\infty f(t)dt$) (IU/ml)*	*Duration of pain (h)*	*Release ratio† (pain) (%)*
Without prior myocardial infarction	34	39·5 ±2·8	939·0 ±99·5	27·3 ±2·3	77·2 ±4·2
With prior myocardial infarction	16	32·4 ±4·4	497·6 ±113·1 *	18·7 ±3·5 *	61·0 ±7·3
Anterior myocardial infarction	23	35·7 ±4·1	719·7 ±122·1	18·9 ±2·6	66·9 ±7·3
without prior myocardial infarction	14	39·5 ±5·5	952·7 ±166·4	23·7 ±3·4	77·6 ±6·9
with prior myocardial infarction	9	29·9 ±5·4	357·1 ±80·1 *	11·4 ±2·4 *	49·5 ±10·6 *
Inferior myocardial infarction	27	38·4 ±2·8	864·3 ±109·1	29·3 ±2·6 **	76·2 ±4·4
without prior myocardial infarction	20	39·5 ±2·7	929·4 ±122·5	29·8 ±2·9	76·9 ±5·4
with prior myocardial infarction	7	35·6 ±7·2	678·3 ±219·1	28·0 ±5·6	74·2 ±7·1
Group A	30	31·2 ±1·9	664·3 ±72·6	22·8 ±2·2	73·3 ±5·1
without prior myocardial infarction	24	33·0 ±2·2	735·3 ±83·6	23·9 ±2·4	74·5 ±5·6
with prior myocardial infarction	6	23·8 ±2·6	380·5 ±54·7 *	18·5 ±4·9	69·0 ±11·6
Group B	20	46·2 ±4·6 **	998·0 ±164·0 **	27·2 ±3·6	79·2 ±5·9
without prior myocardial infarction	10	54·9 ±5·4	1428·0 ±200·4	35·5 ±3·9	83·2 ±5·1
with prior myocardial infarction	10	37·5 ±6·4	567·9 ±174·3 **	18·8 ±4·7 *	55·7 ±8·9
Total	50	37·2 ±2·4	797·8 ±82·0	24·5 ±2·0	72·0 ±3·9

*$P < 0·05$
**$P < 0·01$.
†Ratio of released CK from onset until pain disappears to total CK released.

(2) APPEARANCE FUNCTION AND DEVELOPMENT OF Q WAVES

The appearance function and the serial changes of $\Sigma Q((Q_{II}+Q_{III}+Q_{aVF})/(R_I+S_{aVR}+R_{aVL}))$ in 3 representative cases are shown in Fig. 3. In case 2 (Fig. 3a), ΣQ increased to a maximum 45 hours after the onset (making a plateau thereafter), when 88·2 per cent of the total CK released had already appeared in the circulation. In 2 other cases (cases 24 and 35 in Fig. 3b, 3c), most of the total CK released had been released by the time of maximum ΣQ. In the 14 patients studied, the ratio of cumulated CK released by the time of maximum ΣQ to total CK released was 80·0±6·4 per cent. This shows that the release of CK calculated from the serial determinations of serum CK activity corresponds to the amplitude development of abnormal Q waves. The mean period from the onset to the point of maximum ΣQ in group B with heart failure was 35·5±3·9 hours, which was longer than in group A without heart failure (23·9±2·4 hours, $P<0·05$).

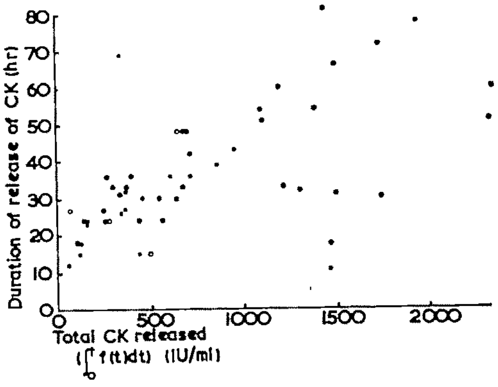

Fig. 2 *Relation between duration of release of CK and total CK released. Closed and open circles represent patients with and without prior myocardial infarction, respectively.*

(3) DURATION OF APPEARANCE FUNCTION AND DURATION OF PAIN

The appearance function of CK and the duration of pain in representative cases are shown in Fig. 1. The mean duration of pain was 24·5±2·0 (3 to 56) hours in the 50 patients. Though this value was 16·4 hours shorter than the mean duration of release of CK, the major release (72·0±3·9% of total CK released) occurred during the period of chest pain. Indeed, in 28 of 50 patients (56%), the difference between the duration of pain and CK release was less than 12 hours.

In the patients with previous myocardial infarction, a smaller per cent of CK (61·0±7·3%) had been released before chest pain disappeared, than in the patients without previous myocardial infarc-

Table 2 *Release ratio of CK in groups A and B*

	Sample size	*Release ratio (peak)† (%)*	*Release ratio (24 h)‡ (%)*
Group A	30	36·5 ±3·3	87·1 ±2·6***
Group B	20	36·4 ±3·9	71·4 ±4·3***
Total	50	36·5 ±2·5	76·7 ±2·3

***$P < 0·005$
†Ratio of released CK until release rate reaches peak to total CK released.
‡Ratio of released CK within 24 hours after onset to total CK released.

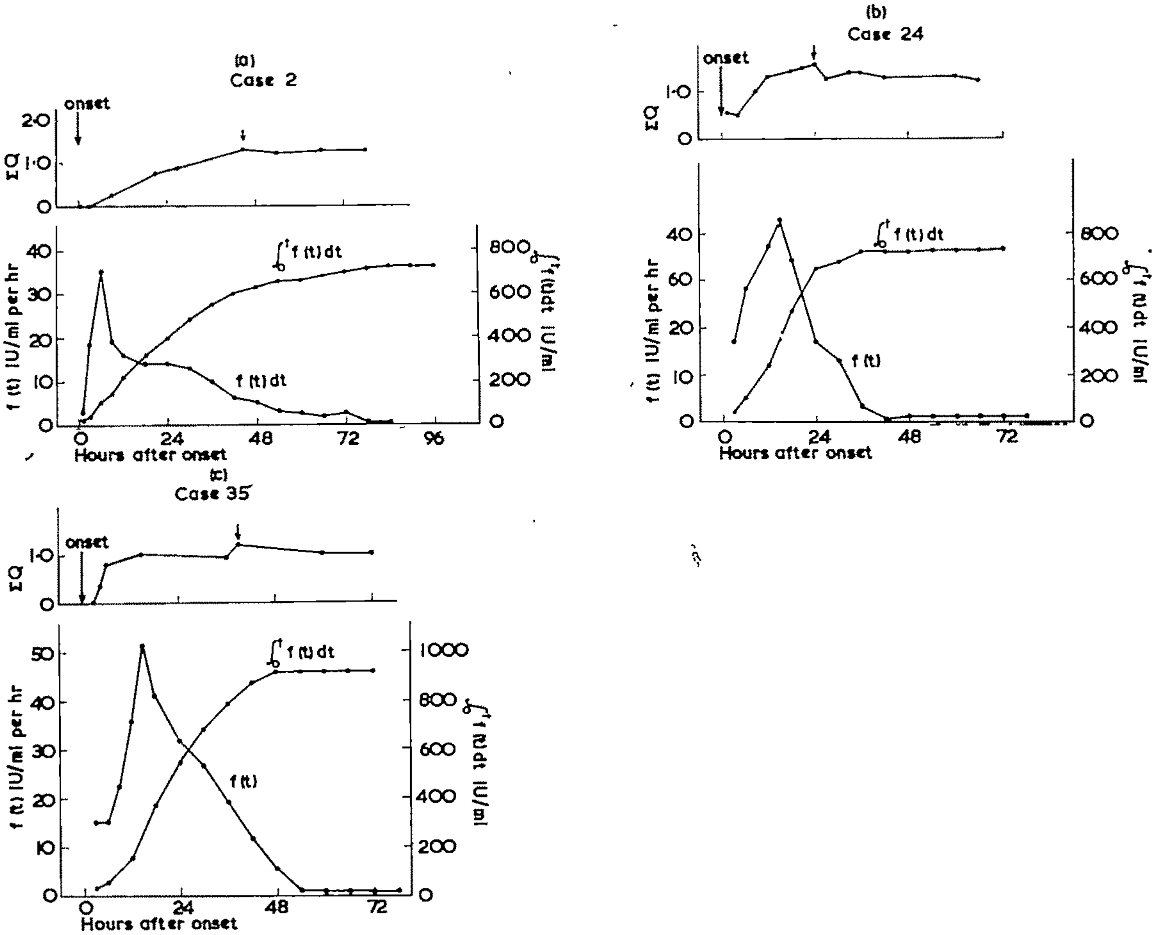

Fig. 3 *Relation between* ΣQ *and appearance function of CK* ($f(t)$) *and cumulated CK released* ($\int_0^t f(t)dt$) *in representative cases.*

tion (77·2 ±4·2% of total CK released). This agrees with the clinical findings that pain stopped earlier in patients with a history of previous myocardial infarction.

The mean duration of pain was shorter in the patients with anterior infarction than in those with inferior infarction in our series. However, if we exclude the patients with previous myocardial infarction, there was no significant difference in the duration of pain between these groups. The mean duration of pain in group B with heart failure was 35·5 ±3·9 hours which was substantially longer than in group A without heart failure.

Discussion

Attempts to achieve reduction of infarct size by pharmacological and physiological interventions have recently been made (Braunwald *et al.*, 1974: Flaherty *et al.*, 1975). To assess these treatments, however, it is necessary to be able to follow the evolution of myocardial infarction as well as to estimate the infarct size. Though Maroko *et al.* (1972a, b) reported the multi-lead electrocardiographic mapping method of assessing the infarct size, individual variations in ST elevation have been shown to be significantly large (Norris *et al.*, 1976). On the other hand, the method of Sobel *et al.* (1972) modified by Norris *et al.* (1975) is very useful in estimating the infarct size from the serial changes of serum CK activity. Though the appearance function calculated by this method represents the evolution of myocardial infarction, there have been few reports relating the appearance function to the clinical course (Mathey *et al.*, 1975).

In the present study, a close relation was observed between the appearance function of CK and chest pain and development of Q waves in the electrocardiogram. This indicates that the evolution of myocardial infarction can be followed by the appearance function of CK.

(1) DURATION OF RELEASE OF CK

The duration of release of CK, calculated by the modified method of Sobel *et al.* (1972), in our series, ranging from 12 to 87 hours, was in good agreement with the report by Sobel *et al.* (1972) and Norris *et al.* (1975). Though the pathological sequential study of the evolution of myocardial infarction in man is impractical, it has been done in dogs. In these experiments there was good agreement between the histochemical findings on the evolution of the infarct (Cox *et al.*, 1968), and the appearance function of CK (Shell *et al.*, 1971). Therefore, the appearance function calculated from the serial serum CK levels should represent the evolution of infarction in man also.

As shown in Fig. 2, the duration of the release of CK correlated well with the total CK released which we know represents the infarct size. This suggests that the larger the infarct, the longer its development requires. This, however, does not agree with the report of Mathey *et al.* (1975) which indicated no significant difference in total CK released between patients with and without prolonged CK release.

(2) DEVELOPMENT OF ABNORMAL Q WAVES

It has been established that the development of abnormal Q waves, initially reported by Pardee (1930), indicates transmural infarction (Myers *et al.*, 1949). In this study serial changes in the amplitude of the pathological Q waves were used as an index of extension of transmural infarction and compared with the appearance function of CK in each case studied. For reliability of measurement of Q waves, patients with anterior infarction, a previous history of myocardial infarction, bundle-branch block, and/or a significant change in electrical axis were excluded from this study. At the time of peak ΣQ (see Method), an average 80 per cent of total CK released had appeared in the circulation (in 13 of the 14 patients, omitting one case with apparently discrepant findings, this was 86%). A pronounced increase in ΣQ was seen in this early phase, corresponding well to the greater release of CK in the first half of the duration of release. Thus, the appearance function of CK can be considered to be in good agreement with the development of the abnormal Q waves. Errors in the peak time of ΣQ were at most 8 hours, since the recording of electrocardiograms was done at least three times a day. However, in one case, ΣQ reached the maximum 6 hours after the onset, while the duration of the release of CK was 36 hours. This may be the result of the gradual extension of nontransmural infarction. In 2 cases, ΣQ curve rose again on the 4th and 5th day after the onset following the initial plateau phase. The late rises in these cases corresponded to changes in the pathological T wave in leads II, III, and aVF, strongly suggesting reinfarction. Poliwoda (1966) found that the amplitude of abnormal Q waves reached a maximum within one week in only about 25 per cent of his patients. In our study, however, ΣQ reached the maximum within 3 days after the onset in 12 of 14 patients. This discrepancy may be the result of the fact that we excluded cases with obvious reinfarction in the acute stage, and also because our ΣQ was obtained by the sum of the amplitudes of Q waves in leads II, III, and aVF corrected by dividing the sum of R_I, S_{aVR}, and R_{aVL}. Indeed without this standardisation, in some cases, the maximum of ΣQ was seen a few days later.

(3) DURATION OF PAIN AND APPEARANCE FUNCTION

In this study, it is suggested that there is a correlation between the duration of pain and that of the release of CK. This agrees with the results reported by Mathey *et al.* (1975), indicating a longer duration of chest pain in patients with prolonged CK release. Though the mechanism of cardiac pain has not been established, pain-producing substances, such as kinin, released by ischaemia are believed to stimulate the nerve endings to cause pain (Gorlin, 1965). Since pain disappears when the ischaemic region has died, the persistence of pain indicates that the extension of the ischaemic zone is continuing (Friedberg, 1966). In 22 of 50 patients, the mean difference between the duration of pain and the release of CK was less than 12 hours, and for all 50 patients an average of 72·0 ±3·1 per cent of the total CK released had appeared in the circulation by the time the pain disappeared. This relation between the duration of pain and the release of CK showed no significant difference between anterior and inferior infarction. However, the duration of pain was shorter in the patients with previous infarction than in those without earlier infarction. Evans and Sutton (1956) also reported that a silent infarction is often seen in patients who have a history of myocardial infarction and/or heart failure. They considered that this may be the result of the slower evolution of infarction in such patients. The fact that there was no difference in the duration of the release of CK between the patients with and without earlier myocardial infarction, in spite of the finding that the mean total CK released in the patients with prior infarction was significantly less than in those without prior infarction, confirms their conclusion. In some cases, the duration of pain was remarkably short showing great discrepancies between it and duration of release of CK. Though this could have been caused by the administration of analgesia, reduction of sensitivity by ageing, and individual subjective variations in complaints of pain, the fact that the mean duration of pain and the maximum time of ΣQ from the onset were shorter than that of the release of CK suggests that the evolution of infarction might be completed a little earlier than the appearance function of CK returning to zero.

(4) VALIDITY OF MATHEMATICAL CALCULATION

Although the method of Sobel and associates which was used in this study is a unique and valuable method, it is based on some assumptions, e.g. that the total amount of CK appearing in the circulation is directly related to the amount lost from myocardium; that the kinetics of enzyme clearance are first order; that the volume of distribution is constant during the evolution of infarction; and that variable inactivation of CK does not occur. These assumptions are open to criticism which if valid would mean that the mathematical model to estimate myocardial enzyme release from the serum CK activites, used in this study, is inaccurate (Roe and Starmer, 1975). While recognising this possibility the correlations observed are none the less significant and potentially useful empirically.

In our study, in order to avoid the effect of extracardiac CK release which would be from traumatised skeletal muscle, all injections were given either intravenously or subcutaneously. Patients with profound haemodynamic alterations, such as cardiogenic shock which could cause a release of noncardiac CK were also excluded. Except in these conditions in which serum CK increases without increasing serum MB-CK activity, the relation between the calculated infarct size from total CK and MB-CK appears to be consistent (Roberts *et al.*, 1975) and the calculated total CK released in this study should reflect the CK released from the myocardium.

In fact, the decrease of serum CK levels after intravenous injection of partially purified CK shows a biphasic curve; the fast and slow components represent the diffusion of CK into a distribution space, and the decaying of total CK, respectively (Shell *et al.*, 1971). In the present method the fractional disappearance rate was calculated from the slope of the monoexponential portion (slow component) of the curve because we cannot obtain the diffusion rate in humans. However, we believe that if the ratio of these two decaying constants are not variable, the ratio of the released CK to the estimated CK released, assuming the first order kinetic, is constant (unpublished data). Therefore, it is reasonable that the actual total CK released can be obtained from the estimated total CK released by multiplying with a correcting factor. In contrast to errors caused by neglecting the fast component of decaying curve in estimating the infarct size, the pattern and duration of the appearance function do not change significantly.

However, the estimated release rate of CK can be affected if the distribution volume changes during the release of CK since the release rate is expressed as the amount of CK which appears in a unit volume (ml) of distribution space in one hour. Recently Witteveen *et al.* (1976) reported the influence of plasma volume change on calculated infarct size, suggesting that the changes in plasma volume have to be taken into account when infarct size is calculated on the basis of serum enzyme levels. Fortunately, however, the characteristics of pattern and duration of the appearance function of CK are not greatly affected by the small change of plasma volume, though the correction of the calculated release rate of CK by haematocrit changes will improve the accuracy of the estimation.

Concerning the invariability of the disappearance rate, Roberts *et al.* (1975) showed that haemodynamic perturbations profoundly affecting cardiac output, heart rate, renal blood flow, or hepatic blood flow in conscious dogs did not much affect the disappearance rate of CK activity, though a wide variation in this measure was observed from person to person. Norris *et al.* (1975) have found that successive determinations of the appearance function are quite constant in the same patient.

Despite the above assumptions which may interfere with the validity of the mathematics of a method, a close relation was observed between the calculated appearance function of CK and the duration of chest pain and the development of Q waves in electrocardiograms which indicate the development of myocardial infarction. Thus, we believe that the estimation of the appearance function of CK is valuable in assessing the development of myocardial infarction and deserves further study.

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Praecordial ST segment elevation

New technique for continuous recording and analysis

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The measurement of praecordial ST segment elevation after myocardial infarction is of value in assessing the natural history of ischaemic injury and the effectiveness of intervention. Hand analysis is, however, time consuming and inaccurate. A technique for continuous recording from 35 praecordial leads and subsequent computer analysis is presented, together with illustrative case studies. Changes in body posture and in heart rate are of importance in subsequent data interpretation.

Interest in attempts to reduce the extent of ischaemic myocardial damage in patients after myocardial infarction and thus to decrease the late incidence of shock and cardiac failure and improve long-term prognosis has led us to reappraise the use of praecordial ST segment mapping as a method of assessing the degree of myocardial ischaemic injury. The technique of praecordial ST segment mapping in man was introduced by Reid *et al.* (1971) and Maroko *et al.* (1972), and is based on experimental work in animals showing a positive correlation between epicardial ST segment elevation early after ligation of a coronary artery and subsequent myocardial damage (Rakita *et al.*, 1954; Maroko *et al.*, 1971; Kjekshus *et al.*, 1972). Though absolute infarct size may not be accurately predicted by this technique (Norris *et al.*, 1976), it is likely that changes in praecordial ST segment elevation, at least in the early hours after infarction, do reflect acute changes in underlying myocardial ischaemic injury. A close correlation has been shown in the dog between the magnitude of praecordial and of epicardial ST segment changes (Muller *et al.*, 1975), and further between epicardial ST segment elevation and changes in local myocardial oxygen tension (Sayen *et al.*, 1961) and blood flow (Kjekshus *et al.*, 1972). The serial measurement of praecordial ST segment elevation should then be of value in assessing both the natural history of myocardial ischaemic injury after infarction and in testing the effectiveness of any pharmacological or metabolic intervention.

The method of praecordial ST segment mapping in common use (Reid *et al.*, 1971; Maroko *et al.*, 1972) is laborious, involving measurements by hand from multiple electrocardiographic recordings. The intermittency of these recordings and the potential subjectivity of the assessment do not allow accurate documentation of spontaneous variations in ST segment elevation, particularly over short periods of time. This knowledge is, however, essential for the accurate interpretation of the results of clinical studies involving therapeutic intervention. For these reasons, we have developed a new technique for the continuous recording of average ST segment elevation and its subsequent measurement by computer.

Technique

LEADS AND ELECTRODES

Thirty-five praecordial leads were used arranged in 5 horizontal rows of 7 according to the method described by Maroko *et al.* (1972) (Fig. 1). The skin was prepared with Cambridge electrode jelly, care being taken not to smear the jelly. Self-adherent electrodes (Devices) were applied, the plastic body of each electrode remaining attached to the permanent lead system; only the adhesive disc was changed between studies.

SYSTEM OF RECORDING

A block diagram of the recording system is shown in Fig. 2a. The lead selector unit allowed signals from individual leads to be examined and recorded separately, and by a matrix of 35 switches corres-

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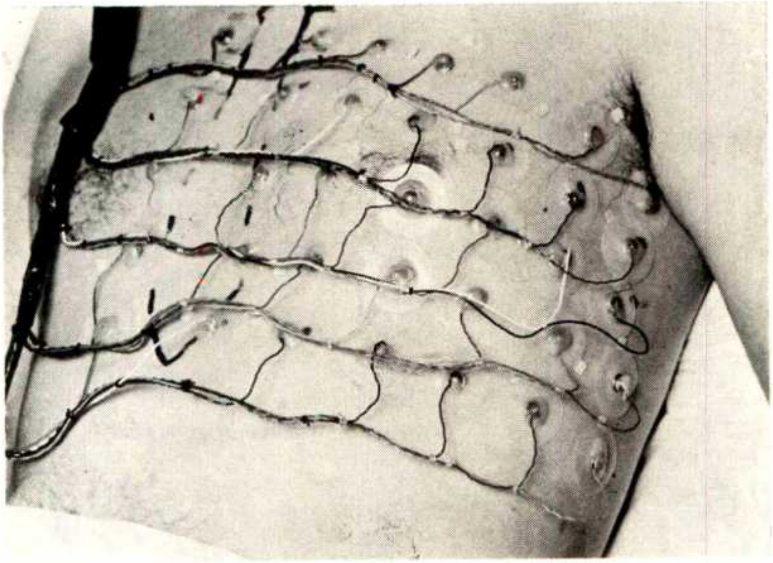

Fig. 1 *The position of the 35 praecordial leads and the self-retaining electrode system* in situ.

ponding to the chest electrode pattern, combined in any combination to produce a 'mean lead' signal. This mean lead signal was formed by summing the selected electrode potentials in a 100 K resistor summing network at the input of a single high input impedance instrumentation amplifier, and then subtracting the reference potential similarly derived from the limb leads. The switching was arranged so that the output thus obtained was the arithmetic mean of the selected electrode potentials with respect to the Wilson central terminal potential. The mean lead signal was then recorded on one of the 3 channels of an FM magnetic tape recorder. The other 2 channels were used to

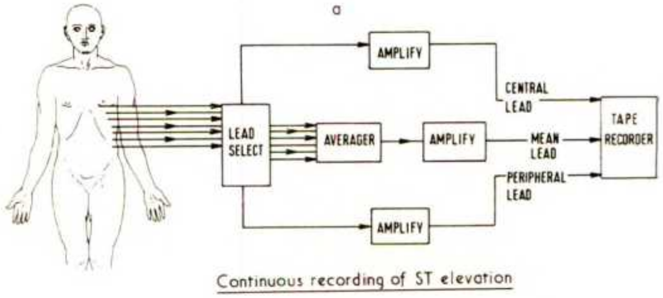

Fig. 2a *A schematic representation of the system for continuous recording of average ST elevation.*

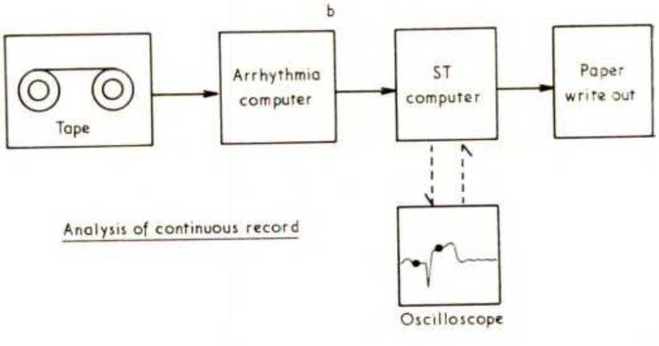

Fig. 2b *A schematic representation of the system of analysis. The ST computer measures the potential difference between the points illustrated on the oscilloscope electrocardiogram.*

record separately any 2 single leads from the 35-lead matrix individually selected at the lead selector unit. The whole system was mounted on a compact trolley which could be wheeled to the bedside (Fig. 3).

Signals from each of the 35 leads were recorded on paper immediately before monitoring and this was repeated at the end of the tape recording period so that changes in the pattern of ST elevation could be recognised as well as changes in magnitude. Leads with more than 1 mm ST elevation were selected for averaging and the 'mean lead' was then continuously recorded on tape together with one central lead (generally the lead showing maximum ST elevation) and one lead from the periphery of the area showing ST elevation. A 1 millivolt calibration signal was included on the mean lead recording for each study.

A typical distribution of ST elevation over the 35 leads from a patient with anteroseptal myocardial infarction is shown in Fig. 4. Representative peripheral and central leads are illustrated and at the bottom of the figure is the mean lead derived from those leads enclosed by the interrupted line.

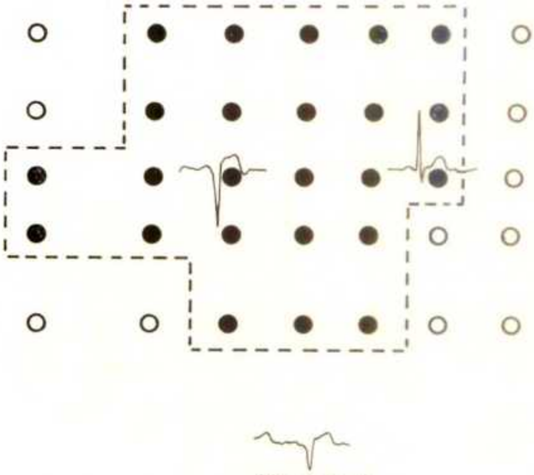

Fig. 4 *A typical distribution of leads showing more than 1 mm ST elevation in a patient with anteroseptal infarction. Representative central and peripheral leads are shown. The lead at the bottom is the mean of all those enclosed by the interrupted line.*

System of analysis

Subsequent analysis of the tape recorded signals was carried out using the system illustrated in Fig. 2b. After calibration of the system, the mean lead signal was replayed from tape at 60 times the original recording speed and analysed using a special purpose arrhythmia computer (Neilson, 1974), which identified each of the normally conducted sinus complexes and rejected those with conducted defects, ventricular extrasystoles, and artefacts. Trigger pulses identifying the normal beats were fed from the arrhythmia computer to

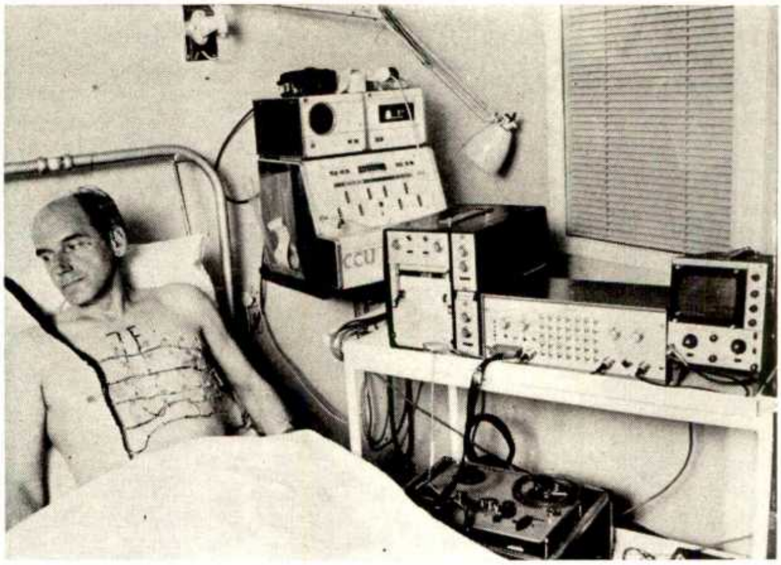

Fig. 3 *The Edinburgh system for continuous recording of ST elevation. The electrodes are in place on the patient's chest. The 'ST averager' is on the top of the trolley with an oscilloscope to its right and a paper recorder to the left. The tape recorder is on the lower shelf.*

the ST computer along with a delayed version of the meaned electrocardiographic signal.

In the ST computer (Neilson *et al.*, 1968) the trigger pulses associated with each electrocardiographic complex control the timing of two samples of the amplitude of the signal voltage at selected instants, each of which is fixed in relation to QRS. Operator controls allow positioning of these sample points. The reference point is positioned in the centre of the isoelectric PR segment and the measurement point on the ST segment between the J point and the upstroke of the T wave. For each complex the ST computer subtracts the voltage at the reference point from that at the measurement point to obtain a measurement of ST elevation for that beat independent of baseline deviations. Each measurement is held in the computer until replaced by that for the next beat, generating a beat-by-beat record of ST elevation, this waveform is smoothed in a low pass filter and the resultant smoothed signal representing the time course of ST elevation is recorded on paper.

The overall system noise in the final record is equivalent to less than 0·004 mV peak-to-peak ST deviation which when processing from a real electrocardiogram is negligible in comparison with natural variation.

Results

COMPARISON WITH HAND MEASUREMENTS

In a preliminary study, 35-lead maps for each of 3 patients were recorded on paper less than 10 minutes before monitoring and again after a period of at least 2 hours of monitoring. The ST elevations greater than 1 mm were selected and measured on both maps for all 3 patients. The measurement point used was 0·06 s after the nadir of the S wave (or the peak of the R waves in leads without an S wave). These measurements were made by each of 5 observers and the summated ST segment elevations obtained for each patient were compared with the corresponding initial and final values derived from the product of the computer mean, which was continuous over the monitoring period, and the number of leads.

The first patient showed a computer value of 89 mm for the initial map and 70 mm for the final map, by comparison with values from hand measurement ranging from 85 to 109 mm (initial map) and 66 to 79 mm (final map). The other two patients showed computer values of 68 mm and 30 mm (initial map), and 49 mm and 45 mm (final map), whereas hand measurements gave values of 51 to 80 mm and 21 to 29 mm (initial map), and 32 to 51 mm and 36 to 42 mm (final map), respectively. The values obtained by the 5 observers differed greatly showing the considerable interobserver variation introduced by the hand method of analysis. In addition, the change in ST elevation between the initial and final maps showed considerable variation between observers: from −19 mm to −30 mm (computer −19 mm) in the first patient; from −19 to −36 mm (computer −19 mm) in the second patient; and from +12 mm to +18 mm (computer +15 mm) in the third patient.

ILLUSTRATIVE CASE STUDIES

Continuous recording and analysis of praecordial ST segment change has been carried out in patients with anterior myocardial infarction within 6 hours of onset of symptoms. Three representative case studies are reported to illustrate the potential application of this technique.

(*a*) *Patient D.G.* (Fig. 5)

This 72-year-old woman was studied from 5½ hours after the onset of chest pain. The standard 12-lead electrocardiogram showed an acute anteroseptal myocardial infarct and the diagnosis of infarction was subsequently confirmed by serum enzyme levels. At the time of study she was free of pain, having received 10 mg morphine intramuscularly 3 hours after the onset of pain. The blood pressure was 170/100 mmHg and the heart rate 80 per min; there were no signs of cardiac failure. She remained free of pain and cardiac failure throughout the 2 hours of study, and received no further

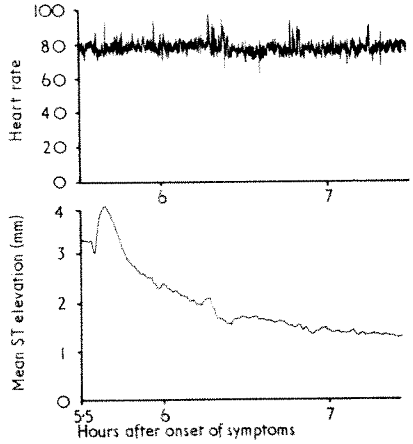

Fig. 5 *Patient D.G. Changes in ST elevation (mean of 13 leads) after acute myocardial infarction without complications or intervention.*

medication; throughout this time she lay flat and slept. The blood pressure on completion of the study was 155/95 mmHg and the heart rate was unchanged.

More than 1 mm ST elevation was found in 13 of the 35 leads at the onset of the study, but in only 5 leads 2 hours later. The average ST elevation from the 13 leads was 3·3 mm initially and had fallen to 1·2 mm by 2 hours. Thus a patient without a major change in clinical state or treatment had a 60 per cent fall in ST elevation over 2 hours.

(*b*) *Patient C.R.* (Fig. 6)

This 56-year-old man was studied from 3 hours after the onset of symptoms. The standard electrocardiogram showed anteroseptal infarction, confirmed by enzyme studies. He had mild chest pain throughout the study but no other complications. One hour before the study he received 10 mg morphine intramuscularly, but no other drugs were administered. When the recording was started he had no signs of cardiac failure and the blood pressure was 120/80 mmHg, with a heart rate of 60 per minute which remained unchanged over the following 2½ hours. More than 1 mm ST elevation was found in 21 leads at the onset of recording. Over the 2½-hour period the mean ST elevation fell from 2·5 mm to 1 mm; thus, in this man a spontaneous fall in ST elevation of 40 per cent took place during this time.

(*c*) *Patient G.C.* (Fig. 7)

This 53-year-old man was monitored from 4 hours after the onset of symptoms. One hour after the chest pain began he required DC conversion from ventricular fibrillation and was started on a lignocaine infusion. The electrocardiogram showed anteroseptal myocardial infarction. Two hours before ST monitoring was started he developed atrial fibrillation and was given digoxin 0·5 mg intravenously one hour later. At the onset of monitoring his blood pressure was 100/70 mmHg and heart rate 130 per min (atrial fibrillation), but there were no signs of cardiac failure. ST elevation of more than 1 mm was found in 24 of the 35 leads. During the period of ST recording he reverted to sinus rhythm, but apart from nausea and vomiting had no further complications. The average ST elevation rose progressively during atrial fibrillation from 3·5 mm at 4 hours to a maximum of 6·7 mm 30 minutes later. There was a short period (at 4 hours 40 minutes) of slowing of the ventricular rate during atrial fibrillation which was accompanied by an abrupt fall in ST elevation. A further abrupt fall occurred at the time of reversion to sinus rhythm, and was followed by a more gradual decline over the ensuing ¾ hour.

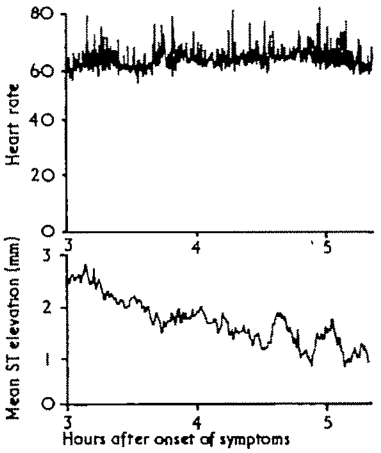

Fig. 6 *Patient C.R. Changes in ST elevation (mean of 21 leads) after myocardial infarction without complications or intervention.*

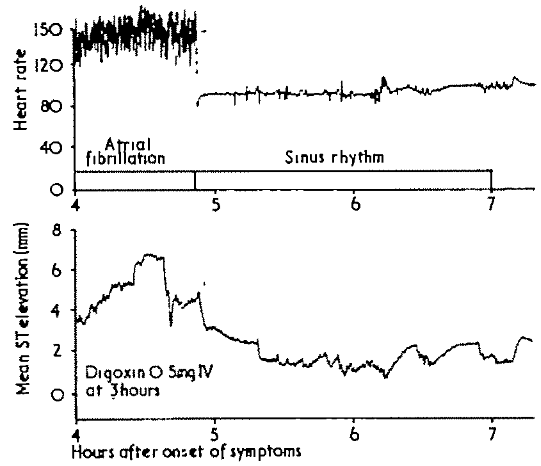

Fig. 7 *Patient G.C. Changes in ST elevation from 4 hours after onset of symptoms of myocardial infarction during atrial fibrillation and after reversion to sinus rhythm.*

EFFECTS OF POSITIONAL CHANGE

Conspicuous variations in recorded ST elevation have been noted as a result of positional change alone, related to a change in direction of the electrical axis of the heart with respect to the chest wall in different body postures. Three illustrative studies are reported.

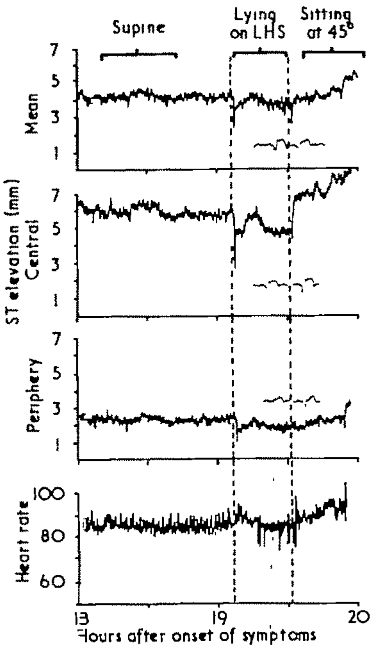

Fig. 8 *Patient G.S. The effect of posture on ST elevation measured from (1) the average of 26 leads, (2) a selected central lead, and (3) a selected peripheral lead. LHS = left-hand side.*

(*a*) *Patient G.S.* (Fig. 8)
This 44-year-old man was studied from 18 hours after the onset of symptoms. There was electrocardiographic and enzyme evidence of anteroseptal myocardial infarction. At the time of the study he was free of pain and clinical signs of cardiac failure. His blood pressure was stable throughout the study at 130/80 mmHg and no drugs were given. For the first hour of recording he remained still and supine, he then turned onto his left side for 25 minutes, and then sat up for a further 30 minutes. A small reduction in recorded ST elevation was seen in the mean lead while lying on his left side. This positional effect was more obvious in the recording from the central lead.

(*b*) *Patients A.H. and A.W.* (Fig. 9a, 9b)
These men, aged 52 and 61 years, respectively, were asymptomatic but showed persistent stable ST elevation from old anterior myocardial infarction. Mapping was performed to show the effect of positional change on the spatial distribution as well as magnitude of ST elevation. Fig. 9a shows the isopotential maps of these 2 patients recorded in a variety of body positions. Fig. 9b shows the summed ST elevations of all 35 leads. Distinct changes occurred, both in the surface distribution and in the sum of ST elevation. Maximum ST

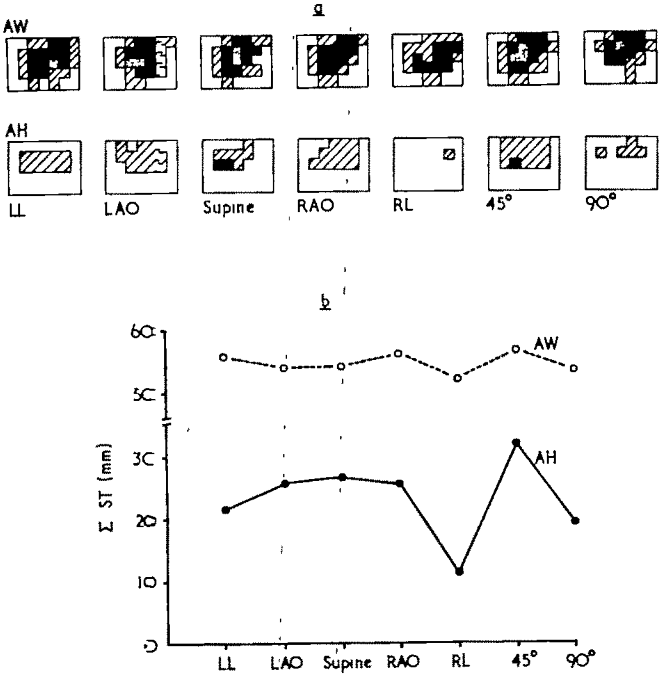

Fig. 9 (*a*) *Isopotential maps in 2 patients with chronic ST segment elevation plotted in 7 different body postures viz left lateral, left anterior oblique, supine, right anterior oblique, right lateral, and sitting at 45° and 90°. Hatched area: over 0·1 mV ST elevation. Solid area: over 0·2 mV ST elevation. Dotted area: over 0·3 mV ST elevation.* (*b*) *Sum of ST elevations in mV in patients shown in Fig. 9a in 7 different body postures.*

elevation was seen in the sitting position at 45°. The shift in electrical axis of the heart was confirmed by concomitant changes in the Q wave vector in both cases.

EFFECT OF CHANGES IN HEART RATE

Striking changes in ST elevation may occur independently of heart rate as in patients D.G. and C.R. (Fig. 5 and 6), but in patient G.C. (Fig. 7) a considerable change in heart rate, as a result of reversion from atrial fibrillation to sinus rhythm, was associated with a similar change in ST elevation. Minor fluctuations in heart rate are at times related to similar minor fluctuations in ST elevation. A transient fall in heart rate in patient D.G. (Fig. 5) at 6 hours was associated with a greater reduction in ST elevation. A transient rise in heart rate in patient C.R. (Fig. 6) at 3 hours was followed by a transient increase in ST elevation. Other fluctuations in heart rate in patient G.C. (Fig. 7) between 6 and 7 hours after onset of symptoms were associated with similar changes in magnitude of ST elevation.

MEAN AND CENTRAL LEADS

In each case computer analysis of the ST elevation has been performed in a meaned complex ('mean lead') and in a 'central' lead (showing maximum ST elevation) and a 'peripheral' lead (showing only 1 mm ST elevation).

A striking similarity was seen between ST recordings from mean and central leads, but the effect of positional change was greater in the recordings from the central lead (Fig. 8). A similarity between mean and peripheral recordings was seen in only some of the cases studied.

Discussion

We have described a new technique whereby accurate continuous analysis of praecordial ST segment change may be made. By contrast, standard methods of praecordial ST segment mapping involve hand measurements from electrocardiograms of 35, 49, or 72 leads (Reid *et al.*, 1971; Maroko *et al.*, 1972; Madias *et al.*, 1975). This is not only laborious, each individual mapping taking 10 or 15 minutes to complete, but also subject to considerable observer variation. In our 3 cases in whom a comparison was performed between hand measurement and computer analysis there were large differences between the results obtained by 5 observers, both for the absolute level of ST elevation and for the change in ST elevation over a period of 2 hours. Under these conditions the significance of sequential changes in ST elevation must be questioned. A further major disadvantage of the hand mapping technique is the necessity for intermittent data sampling. Our system of computer analysis which can measure mean ST elevation on a beat-by-beat basis has shown that major fluctuations in ST segment change may occur over short periods of time. Patient G.C. (Fig. 9), for example, showed a reduction in ST elevation of over 70 per cent in under 1 hour. In this case 15- or 30-minute sampling would have failed to reveal major changes in ST segment shift. It is known that rapid changes in coronary perfusion and myocardial oxygen tension may occur in the early hours after infarction, yet evidence from conventional ST mapping has been contradictory; thus, it has been claimed that the rate of ST segment change is small (Madias 1975) or very variable (Reese *et al.*, 1973). Continuous analysis also reveals the occurrence of minor fluctuations in ST elevation, related to transient changes in heart rate, so providing an extremely sensitive index of underlying electrophysiological changes of myocardial ischaemia.

Conventional hand mapping, however, does make it possible to analyse sequential changes in distribution of ST segment shifts with delineation of areas of ST segment elevation and of ST segment depression. The latter are excluded from our system of computer analysis by the initial lead selection procedure. These spatial analyses can be performed at any selected time during monitoring by direct recording on paper. In the absence of complex modifications of the recording and computing system such information can only be obtained intermittently and is limited by the number of recording electrodes. Our measurements of mean ST segment elevation from a fixed number of praecordial leads may result in a certain loss of information as a result of spatial change in ST segment shifts. Voltage change itself, however, is partly dependent upon underlying spatial changes in distribution of ischaemic injury, and it is not clear what additional information may be obtained from a separate continuous spatial analysis.

Computer analysis of continuously recorded data provides highly accurate and easily reproducible data. The noise level of our system allows for a measurement of ST elevation to an accuracy of 0·004 mV. The usefulness of this information is, however, limited by the inherent limitations of praecordial mapping itself. Excellent correlation has been shown in the dog between praecordial and epicardial ST elevation (Muller *et al.*, 1975), and changes in epicardial ST elevation after acute coronary occlusion have been correlated with subsequent creatine kinase depletion (Maroko *et al.*, 1971), changes in local myocardial oxygen tension (Sayen *et al.*, 1961), blood flow (Kjekshus *et al.*, 1972), and potential gradients (Prinzmetal *et al.*, 1962). The situation in man is more complex. Infarction may not be the result of a single discrete coronary occlusion and patients are not studied until some hours after onset of symptoms. Praecordial mapping is limited to cases of anterior or anteroseptal infarction who may well have additional inferior, posterior, or lateral injury, not contributing to praecordial ST segment change. In addition the 35 chosen lead positions may not subtend the whole of the injured and potentially injured area. Other factors than ischaemia are well known to affect ST segment elevation, in particular pericarditis, conduction defects, sympathetic stimulation, temperature change, and drugs such as quinidine and digitalis.

It is likely that at least in the early hours after infarction praecordial ST elevation does reflect the electrophysiological properties of the underlying epicardium, in turn related to the degree of ischaemia. The spontaneous changes in mean ST elevation shown in the 3 illustrated cases all studied within 6 hours of the onset of chest pain probably reflect changes in severity of ischaemic injury. Our initial studies, however, have emphasised some difficulties which arise in interpreting these data. It is well known that the electrical axis of the heart with respect to the chest wall varies with body posture and indeed with respiration. It is apparent that the same is true for the ST segment. Patients A.H. and A.W. (Fig. 5) show the enormous variations in both spatial distribution of elevated ST segments and in mean ST elevation that may occur in a variety of body postures. Any interpretation of ST segment change must then be dependent upon an exact knowledge of body position. Merely sitting forward to sip a cup of tea is associated with a minor transient change in recorded mean ST elevation.

Similarly increases in heart rate are at times associated with increased ST segment elevation. This may result partly from the effect of changes in heart rate on the QT interval, affecting the upward slope of an ST segment. It is more likely, in view of the haemodynamic effect of changes in heart rate on coronary blood flow, that these directly influence the imbalance between oxygen supply and demand in the ischaemic myocardium.

The observation that changes in ST elevation in the mean lead are similar to those in the single central lead showing maximum ST elevation is of practical interest in that, if as much useful information is contained in a recording from a single lead as from 35, the computer analysis technique may have an application in other than specialist centres. The single lead is more affected by changes in body posture (Fig. 8) than is the mean lead; the significance of measurements of ST elevation obtained from it requires further evaluation.

Interest has grown in recent years in the possibility that pharmacological or metabolic intervention after myocardial infarction may reduce the degree of myocardial ischaemic injury, and it has been suggested that measurement of praecordial ST elevation may be of use in testing the efficacy of such therapy (Pelides *et al.*, 1972). It is apparent, however, that before any such study is possible knowledge of the natural course of ST segment change is necessary. Our technique of continuous recording and analysis is a significant advance on existing techniques and is ideally suited for study of the natural history of ST segment change. It is presented as an objective research tool which is likely to be of particular value when assessing the effects of intervention after myocardial infarction.

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Primary ST changes
Diagnostic aid in paced patients with acute myocardial infarction

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In 34 out of 36 patients with apical right ventricular endocardial pacing, primary ischaemic ST alterations were observed during the early stage of acute myocardial infarction. These ST changes, indicating acute injury, were detected in the paced beats in inferior and in anterior infarct. The primary ST changes were consistent only during the early stages of acute myocardial infarction and were not detected when the electrode tip was not in the apex of the right ventricle. It is suggested that the primary ST changes should be used to diagnose acute myocardial infarction in paced patients.

The diagnosis of acute myocardial infarction in patients with implanted pacemakers is difficult and has remained an electrocardiographic diagnostic problem. Previous attempts to resolve this difficulty were based on the following concepts:

(1) Analysis of escape beats or of the instrinsic rhythm by means of continuous monitoring or by various electrical interventions in pacemaker function (Center *et al.*, 1971; Bathen and Abrahamsen, 1973).

(2) Applying the same criteria used to diagnose myocardial infarction in the presence of complete left bundle-branch block (Sodi-Pallares *et al.*, 1963) to the paced QRS complexes (Cardenas *et al.*, 1972; Castellanos *et al.*, 1973). However, it was found that the changes in the paced QRS were not consistent, especially in cases of inferior myocardial infarction (Barold *et al.*, 1976).

Rothfeld *et al.* (1973) described ischaemic ST-T alterations in paced days in whom myocardial infarction was induced by ligation of coronary arteries. They noticed large ST vectors oriented toward the site of infarction, reflecting an injury pattern similar to those seen in non-paced patients with or without intraventricular conduction defects. These ST-T changes were present in all paced dogs with infarction.

The purpose of this study was to measure the incidence of the ischaemic ST alterations in paced patients during the acute phase of myocardial infarction, in order to assess their reliability as a method of diagnosing acute myocardial infarction in patients with permanent pacing.

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Subjects and methods

Studies were made on 45 patients with acute myocardial infarction who were admitted to the coronary care unit. The diagnosis of acute myocardial infarction was confirmed in all patients by clinical, electrocardiographic, and enzymatic criteria. A temporary pacemaker was inserted in all these patients because of the development of 2nd and 3rd degree atrioventricular block or trifascicular block during the acute phase. The transvenous bipolar electrode was introduced into the right ventricle under fluoroscopic control through the antecubital or jugular veins. The external pacemaker used was Medtronic model No. 5880. In 41 patients the tip of the electrode was placed in the apex of the right ventricle, in 2 patients it was found to be in a mid-ventricular position, and in another 2 patients in the outflow tract. The site of infarction was as follows: anterior wall—15 patients, inferior wall—16, inferior and true posterior—12, anterior and inferior—2 patients. In cases with complete atrioventricular block, the electrocardiographic diagnosis of acute myocardial infarction was always made before the development of this conduction disturbance. Thus, in all the patients the information about the phase and the site of infarction was obtained by the analysis of conducted sinus beats. A routine 12 lead electrocardiogram was obtained twice daily during pacing, and during interruption of pacing, unless contraindicated.

Results

Ischaemic ST-T changes were considered to be diagnostic if ST elevation was at least 2 mm with a convex shape. Such transient changes during the acute phase of myocardial infarction were found in 34 patients out of the total group of 45 (Fig. 1 and 2).

During the study we realised that patients in phase III of the electrocardiographic evolution of acute myocardial infarction, or with the electrode tip not situated at the apex (Fig. 3) did not show these typical ischaemic ST-T alterations. Nine such patients (7 in phase III and 2 with the electrode tip not at the apex) were excluded from the total number of patients. In order to determine the phase of the electrocardiographic evolution of acute myocardial infarction, we have used the following accepted classification which differentiates four phases (Rushmer, 1955): Phase I is characterised by a prominent ST elevation and a positive or biphasic T wave and phase II by a pathological q wave, a less prominent ST elevation, and an inverted T wave. In phase III, the ST segment is iso-electric, the T wave is inverted and the q wave is more pronounced. The electrocardiographic evolution might end at this phase or can proceed to phase IV, in which the T wave returns to normal. The time interval from phase I to phase II ranges between a few minutes and several hours and from phase II to phase III between a few hours and several days. Thus, in 34 of the remaining 36 patients (94·4%) ischaemic ST-T changes were diagnostic of acute myocardial infarction during pacing. In only 2 patients were these changes not observed though the tip of the electrode was at the apex and the electrocardiographic phase was I or II, and should, therefore, be considered false negatives. The ischaemic ST-T alterations during pacing were always located in the same leads in which they appear on conducted sinus beats (Fig. 1 and 2).

Discussion

Sodi-Pallares *et al.* (1963) were the first to describe the patterns of myocardial infarction in the presence of complete right or left bundle-branch block. By applying the same criteria used by Sodi-Pallares *et al.* (1963) several electrocardiographic patterns were recently described as diagnostic of myocardial infarction in the presence of right ventricular pacing, based on the similarity between the morphology of complete left bundle-branch block and the paced QRS. Cardenas *et al.* (1972) described an initial R in aVR and V1 for inferior and true posterior myocardial infarction, qR in V5 and V6 for antero-septal myocardial infarction, and RS in V5 and V6 for lateral myocardial infarction. Castellanos *et al.* (1973) described a St-qR pattern in lead I, aVL, V5, V6 for anteroseptal myocardial infarction and pointed out that these changes in QRS might be overlooked or even absent when unipolar stimulation is used. The distortion that large unipolar spikes can produce might make it difficult to determine whether the finding is an artefact or a true reflection of an alteration in ventricular activation. Barold *et al.* (1976) did not agree with the specificity of Cardenas's criteria for inferior myocardial infarction and suggested that a qR pattern in the inferior leads is a more specific though rare sign of inferior myocardial infarction during right ventricular pacing. In summary, the patterns described are inconsistent and their significance is controversial.

Rothfeld *et al.* (1973) showed recently that in all paced dogs with experimental acute myocardial infarction, large ST vectors oriented toward the site of infarction were observed even during pacemaker rhythm. In the present study we have shown that primary ischaemic ST elevation can be also seen in a high percentage of paced patients during the acute phase of infarction. During right ventricular endocardial pacing as in complete left bundle-branch block, it is the septal depolarisation that determines the direction of the AQRS and therefore also the direction of the AST and AT. Thus, the ST changes seen during right ventricular pacing and in complete left bundle-branch block are of the secondary type, reflecting a disturbed depolarisation. In the presence of acute myocardial infarction, it is the site of the injured area (epicardial or endocardial) that determines the direction of the ST vector and its shape. If both ST vectors (primary and secondary) coincide in direction, there will be exaggeration of the ST displacement. On the other hand, if these vectors are opposed, the final ST displacement will be minimal or even absent. For example, in paced patients with inferior acute myocardial infarction, both ST vectors are oriented toward the same direction, causing exaggeration of the convex ST elevation in leads II, III, and aVF (Fig. 1). The same findings can be observed in leads V1 to V4 in anteroseptal acute myocardial infarction (Fig. 2). However, in anterolateral acute myocardial infarction there is an opposition between

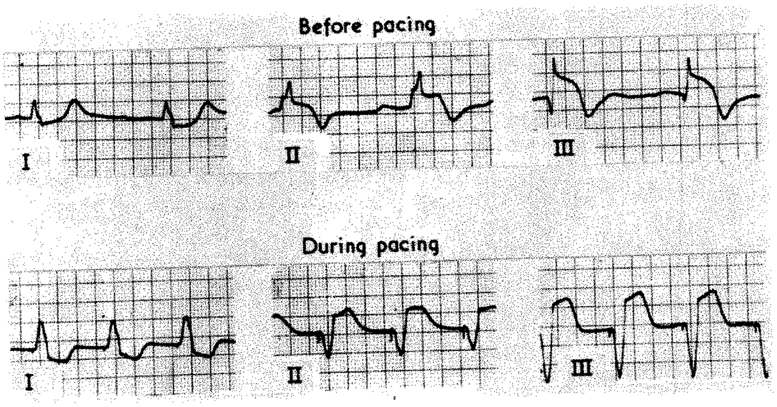

Fig. 1 *Acute inferior myocardial infarction. Ischaemic ST elevation is present in the same leads, before and during pacing.*

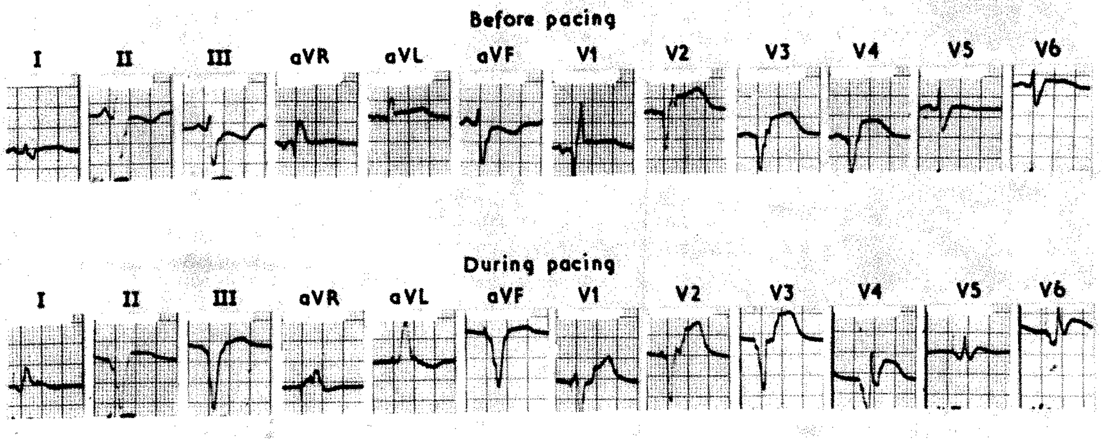

Fig. 2 *Acute anterior myocardial infarction. Ischaemic ST elevation is present in conducted sinus beats and in the paced beats. The diagnostic QRS criteria are also present (q wave in lead I, aVL, V4 to V6).*

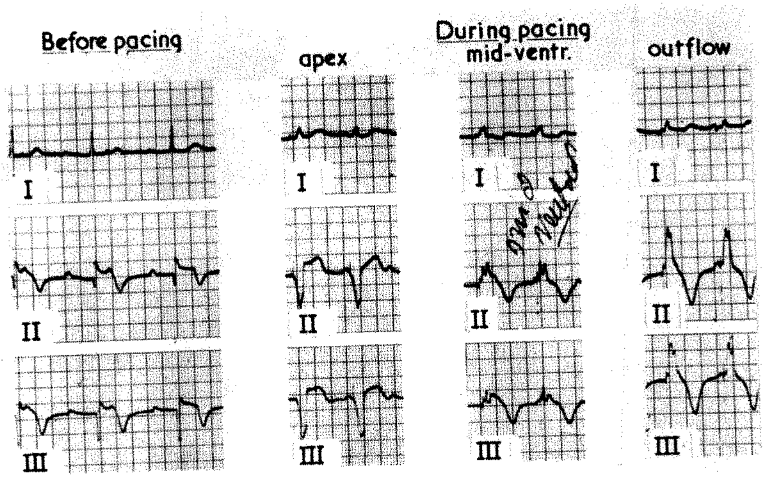

Fig. 3 *Acute inferior infarction. The electrode tip was transferred from the right ventricular apex to the mid-ventricle and outflow tract regions. During apical pacing, primary ST elevation is detected in leads II and III, but at both other tip positions it is masked by the shift to the right of the AQRS.*

the 2 vectors and, therefore, the typical diagnostic ST elevation can be detected only during the initial stage of electrocardiographic evolution, when the disturbed electrophysiological activity of the injured area is still predominant.

The AQRS, and therefore the AST, is also determined by the site of the electrical stimulation at the right ventricle. When the electrode tip is at the apex, the AQRS is usually −60° or more to the left. However, if the tip is located at mid-ventricular region or at the outflow tract, the AQRS shifts to the right. This causes a secondary displacement of the ST segment which is opposed to the direction of the primary ST vector, and, therefore, may mask the typical injury pattern (Fig. 3).

In summary, we found in this study that primary ST changes, suggesting acute injury, are present during the early stage of infarction in almost all patients undergoing right ventricular apical pacing. We suggest the use of these ST changes as a diagnostic aid for detection of the acute event in paced patients.

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Atrial pacing at multiple sites in the Wolff-Parkinson-White syndrome[1]

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Atrial pacing at multiple sites was used in an attempt to predict the site of pre-excitation in 5 patients with Wolff-Parkinson-White syndrome with 5 different anomalous pathway locations (right anterior, right posterior, septal, left posterior, and left lateral). At least 3 atrial pacing sites were tested in each patient. Pacing sites tested included high right atrium, low lateral right atrium, low septal right atrium, proximal coronary sinus, and distal coronary sinus. Atrial stimulation sites with shortest and longest stimulus-delta intervals could be identified in each patient, the shortest stimulus-delta interval in each case ranging from 60 to 80 ms. The difference between the shortest and longest stimulus-delta interval in each case ranged from 60 to 110 ms. It was suggested that the site with the shortest stimulus-delta interval corresponded to a site close to the atrial insertion of the anomalous pathway. This hypothesis was confirmed in all cases (3 with epicardial mapping and 2 with retrograde atrial activation data). In conclusion, atrial pacing at multiple sites is helpful in predicting the site of anterogradely conducting anomalous pathways, and appears particularly useful for differentiation of right posterior, left posterior, and septal pre-excitation.

Cure of Wolff-Parkinson-White syndrome is now possible using epicardial mapping for delineating the site of pre-excitation, and surgical transection of anomalous AV connections (Sealy and Wallace, 1974; Gallagher *et al.*, 1975). Anomalous pathway location plays a role in determining the success of operation (Sealy and Wallace, 1974; Gallagher *et al.*, 1975; Tonkin *et al.*, 1975). Right anterior, lateral, and posterior as well as left lateral anomalous AV connections appear readily accessible to surgical cure. Left posterior and septal anomalous pathways are less accessible to the surgeon. Since, therefore, the surgical cure of pre-excitation appears to be partly related to anomalous pathway location, the accurate preoperative localisation of these pathways has assumed considerable importance.

The means of predicting anomalous pathway locations include surface electrocardiography and vectorcardiography, as well as electrophysiological evaluation in the catheterisation laboratory (Wellens *et al.*, 1971; Touboul *et al.*, 1972; Coumel and Attuel, 1974; Denes *et al.*, 1974; Spurrell *et al.*, 1974; Svenson *et al.*, 1974, 1975; Wellens and Durrer, 1974, 1975; Wyndham *et al.*, 1974; Zipes *et al.*, 1974; Gallagher *et al.*, 1975; Neuss *et al.*, 1975; Denes *et al.*, 1976a, b). Electrophysiological techniques include lateralisation of the anomalous pathway by noting the effects of functional bundle-branch block on the cycle length of circus movement tachycardia or on retrograde anomalous pathway conduction time (Coumel and Attuel, 1974; Spurrell *et al.*, 1974; Zipes *et al.*, 1974; Neuss *et al.*, 1975; Wellens and Durrer, 1975); intracardiac catheter electrode mapping of retrograde atrial activation during circus movement tachycardia and/or with ventricular pacing (Svenson *et al.*, 1974, 1975; Wellens and Durrer, 1974, 1975; Zipes *et al.*, 1974; Gallagher *et al.*, 1975; Neuss *et al.*, 1975; Denes *et al.*, 1976a, b), and evaluation of atrial pacing at multiple sites with observation of QRS morphology and stimulus-delta intervals (Wellens *et al.*, 1971; Touboul *et al.*, 1972; Denes *et al.*, 1974; Gallagher *et al.*, 1975; Svenson *et al.*, 1975; Denes *et al.*, 1976a).

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Although all these techniques appear to be of value in localisation of anomalous pathways, major emphasis has been placed upon the use of retrograde atrial activation sequences in the prediction of anomalous pathway location (Zipes *et al.*, 1974; Wellens and Durrer, 1974, 1975; Gallagher *et al.*, 1975; Neuss *et al.*, 1975; Svenson *et al.*, 1975; Denes *et al.*, 1976a). The use of atrial pacing at multiple sites has received less attention. In the present study, we describe the results of atrial pacing studies at multiple sites in 5 patients with anterogradely conducting anomalous pathways in different locations. Our results confirm the value of multiple atrial pacing sites in anomalous pathway localisation. In addition, criteria are developed for using the information obtained with this technique in predicting the site of pre-excitation.

Methods

Five patients with pre-excitation were selected for presentation in this report. All patients had typical surface electrocardiographic findings of Wolff-Parkinson-White syndrome including a short PR interval (less than 0·12 s), wide QRS complexes (0·12 s or greater), delta waves, and documented supraventricular tachyarrhythmias. These 5 patients were selected because: (1) technically adequate multiple atrial pacing site data were obtained for analysis, and (2) the anomalous pathway location was reasonably well documented, so that the predictive value of multiple atrial pacing sites could be examined. (3) The patients represented 5 different anomalous pathway locations.

Electrophysiological studies were performed in the supine, non-sedated state. Informed written consent was obtained from all patients before the study. All cardioactive drugs were discontinued 48 hours before the study. Catheter techniques for recording and stimulation were similar to those previously described (Wyndham *et al.*, 1974; Denes *et al.*, 1976a, b). Electrocardiographic leads I, II, III, and V1, atrial and His bundle electrograms were recorded using a paper speed of 100 mm/s. Intervals were measured by averaging 10 consecutive beats. Tripolar and quadripolar catheters (with interelectrode distances of 1 cm) were placed under fluoroscopic control.

The following atrial pacing sites were used: (1) high right atrium, at the superior vena cava-right atrial junction, (2) low lateral right atrium, at the inferior vena cava-right atrial junction, (3) low septal right atrium (using the His bundle recording catheter) at the most distal site on pull-back from the ventricle, where stable atrial capture with an atrial depolarisation preceding the QRS complex could be obtained, (4) right atrial appendage, (5) proximal coronary sinus (just inside the os of the coronary sinus), (6) distal coronary sinus (at the most distal site in the coronary sinus where atrial capture could be obtained, usually close to the left heart border).

The atria were stimulated from the tested sites at rates slightly faster than sinus and then in 10 beats/minute increments until total pre-excitation was achieved. The stimulus-delta remained constant at increasing pacing rates. For purposes of comparison results in each case were compared at an identical cycle length between 460 and 600 ms. Epicardial mapping techniques were similar to those previously described by our laboratory (Wyndham *et al.*, 1974; Denes *et al.*, 1976a, b).

DEFINITIONS

Pre-excitation was classified electrocardiographically during maximal pre-excitation. The electrocardiographic classification of pre-excitation was based on the work of Boineau *et al.* (1973).

Anterior right ventricular pre-excitation (type B) was defined by the presence of a QS or rS in V1 and an R in I and III. Posterior right ventricular pre-excitation (type AB) was defined by the presence of a QS or rS in V1, an R in I, and a QS in III. Posterior left ventricular pre-excitation (type A) was defined by the presence of an R or RS in V1, an R in I, and a QS or rS in III. Lateral left ventricular pre-excitation (type C) was defined by the presence of an R or RS in V1, a QS or rS in I, and an R in III.

Stimulus-delta intervals were measured from the onset of the stimulus artefact to the earliest onset of the delta wave on simultaneous surface electrocardiographic leads. This interval represented the atrial and anomalous pathway conduction times from the site of atrial stimulation.

Total or maximal pre-excitation referred to a QRS complex resulting from ventricular activation exclusively through the anomalous atrioventricular connection.

Results

CASE 1

The patient was a 25-year-old woman with symptomatic recurrent paroxysmal supraventricular tachycardia and recurrent paroxysmal atrial fibrillation with rapid ventricular response. Electrocardiograms revealed type B pre-excitation (Fig. 1). Basic conduction intervals were recorded during sinus rhythm at a cycle length of 610 ms and revealed a PA interval of 30 ms. AH and HV intervals could not be measured since the His bundle electrograms were buried within the ventricular electrogram. The P delta interval was of 75 ms.

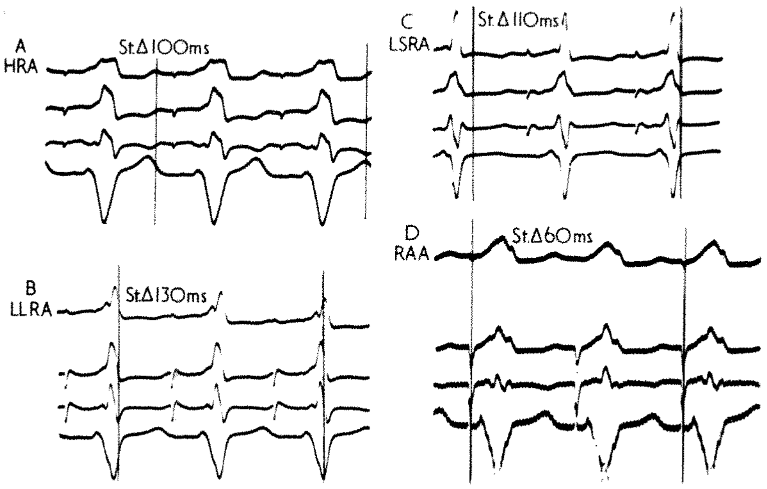

Fig. 1 *The effect of atrial pacing at multiple sites on stimulus-delta intervals in case 1 with type B pre-excitation. Shown in each panel from top to bottom are surface electrocardiographic leads I, II, III, and V1. HRA represents high right atrial pacing; LLRA low lateral right atrial pacing; LSRA low septal right atrial pacing; RAA right atrial appendage pacing. Cycle length was 500 ms. Stimulus-delta intervals are listed and expressed in ms. Time lines are at 1 second and paper speed is 100 mm/s in this and subsequent illustrations. Note that the shortest stimulus-delta interval (60 ms) is obtained with right atrial appendage pacing (panel D).*

Four atrial pacing sites were studied at a cycle length of 500 ms. The stimulus-delta intervals and QRS durations from these sites were as follows: (1) high right atrium, with a stimulus-delta of 100 ms and QRS duration of 180 ms (Fig. 1A); (2) low lateral right atrium, with a stimulus-delta of 130 ms and a QRS duration of 150 ms (Fig. 1B); (3) low septal right atrium with a stimulus-delta of 110 ms and QRS duration of 130 ms (Fig. 1C); (4) right atrial appendage, with a stimulus-delta of 60 ms and QRS duration of 180 ms (Fig. 1D).

Curative surgery was attempted because of recurrent tachyarrhythmias. Epicardial mapping revealed earliest ventricular activation on the anterior right ventricle adjacent to the right atrial appendage (Fig. 2). The epicardial ventricular electrograms preceded the onset of the delta wave by 38 ms. After epicardial mapping, the right atrium was entered during cardiopulmonary bypass. A transmural atrial incision was made parallel to the AV ring and adjacent to the area of earliest ventricular activation. All subsequent electrograms have revealed normal PR intervals without pre-excitation. Arrhythmias have not recurred (6-month follow-up).

Comment

Electrocardiograms before surgery suggested a right anterior anomalous pathway. Atrial pacing studies at multiple sites provided strong evidence of an anterior right AV connection with demonstration of the shortest stimulus-delta interval (60 ms) and maximum pre-excitation from the right atrial appendage pacing site. The predicted site of pre-excitation was confirmed at cardiac surgery.

CASE 2

This was a 15-year-old youth with recurrent paroxysmal supreventricular tachycardia. Electrocardiograms during total pre-excitation revealed type AB pre-excitation. This case has been previously reported because of bilateral anomalous pathways (a manifest right posterior anterograde pathway, and a left lateral concealed retrograde pathway), and will, therefore, be described only briefly here (Denes *et al.*, 1976a).

Three atrial pacing sites were studied at a cycle length of 600 ms (Fig. 2 of Denes *et al.* (1976a)). The stimulus-delta intervals and QRS duration from these sites were as follows: (1) high right atrium, with a stimulus-delta of 140 ms and QRS duration of 120 ms; (2) low lateral right atrium, with a stimulus-delta of 80 ms and QRS duration of 180 ms; (3) proximal coronary sinus, with a stimulus-delta of 115 ms and QRS duration of 170 ms. Epicardial mapping revealed early activation of the posterior right ventricle contiguous to the intraventricular groove, with early activation coinciding with the onset of the delta wave (Fig. 6 of Denes *et al.* (1976a)). A transmural right atrial incision parallel to the AV ring adjacent to the site of earliest ventricular activation resulted in cure of anterograde pre-excitation.

Comment

In this patient, the electrocardiogram during total pre-excitation suggested a posterior right ventricular connection. The atrial pacing site study showed the shortest stimulus-delta and widest QRS complex from the low lateral right atrium suggesting a lateral right atrial connection. The posterior right atrium was not tested. Epicardial mapping studies and surgery localised the anterogradely conducting anomalous connection to the right posterior ventricle.

CASE 3

This was a 37-year-old man with recurrent paroxysmal supraventricular tachycardia. Electrocardiograms during total pre-excitation indicated type AB pre-excitation (Fig. 3).

Basic conduction intervals were recorded during sinus rhythm at a cycle length of 870 ms and were as follows: P delta of 100 ms and PA of 30 ms. AH and HV intervals could not be measured since the H potential was buried within the ventricular electrogram.

Four atrial pacing sites were selected for pacing at a cycle length of 460 ms. The stimulus-delta intervals and QRS duration from these sites were as follows: (1) High right atrium, with a stimulus-delta of 110 ms and QRS duration of 170 ms (Fig. 3A). (2) Low lateral right atrium, with a stimulus-delta of 110 ms and QRS duration of 170 ms (Fig. 3B). (3) Low septal right atrium, with a stimulus-delta of 70 ms and QRS duration of 170 ms (Fig. 3C). (4) Distal coronary sinus, with a stimulus-delta of 140 ms and QRS duration of 170 ms (Fig. 3D).

Retrograde atrial activation sequences were determined during right ventricular pacing. Low right atrial septal electrograms preceded high right atrial, lateral right atrial, and right atrial appendage electrograms by 30, 40, and 50 ms, respectively. The retrograde conduction time measured from the onset of the QRS to the low septal right atrial electrogram was 90 ms and was constant at all ventricular paced cycle lengths.

Comment

The electrocardiogram in this patient was similar to that of case 2 and suggested a posterior right ventricular connection. However, atrial pacing site studies strongly suggested a septal anomalous pathway, because of the very short stimulus-delta with low right atrial septal pacing. Though this anomalous pathway location was not confirmed with epicardial mapping and surgery, the retrograde activation data provided strong confirmatory evidence for this predicted site of pre-excitation (Gallagher *et al.*, 1975). These electrophysiological findings led to a decision not to attempt surgical cure of the pre-excitation.

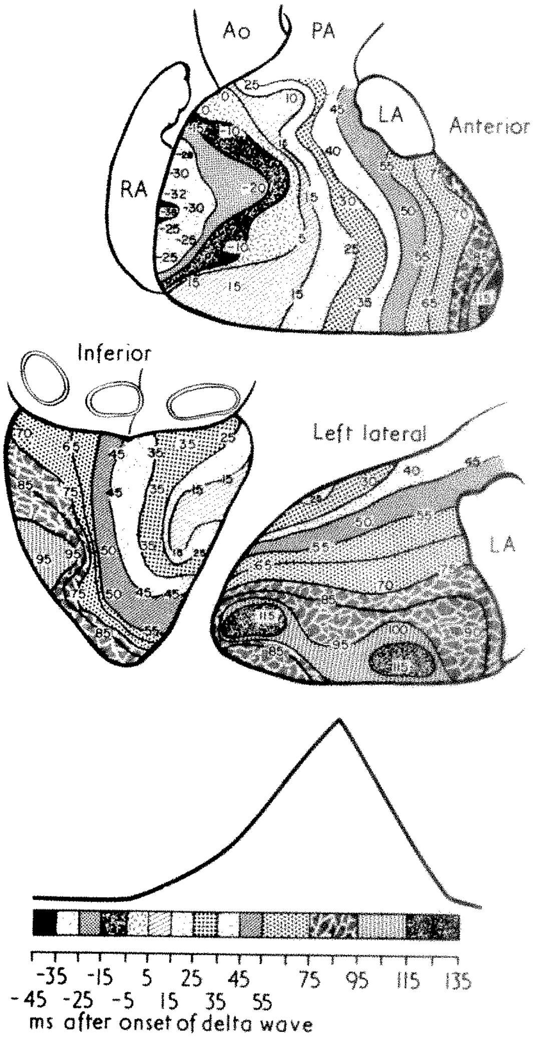

Fig. 2 *Diagram of epicardial activation during pre-excitation in case 1. Isochronous lines are drawn at 10 to 20 ms intervals with reference to the onset of delta wave. Inferior (upper), anterior (lower left), and left lateral (lower right) views of the heart are shown. The earliest area of epicardial activity is on the posterolateral left ventricle.*

CASE 4

This was an 18-year-old youth with paroxysmal atrial fibrillation. Electrocardiograms revealed type A pre-excitation (Fig. 4). Basic conduction intervals at a cycle length of 765 ms revealed a P delta of 120

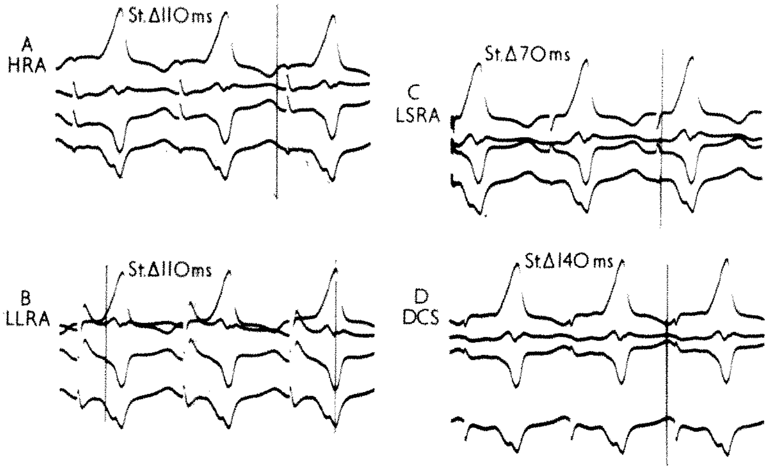

Fig. 3 *The effect of atrial pacing at multiple sites on stimulus-delta intervals in case 3 with type AB pre-excitation. In each panel surface electrocardiographic lead I, II, III, and V1 are shown. Abbreviations are similar to Fig. 1. DCS represents distal coronary sinus pacing. Note that the shortest stimulus-delta interval (70 ms) is obtained with low septal right atrial pacing.*

ms, PA of 24 ms, AH of 53 ms, and an HV of 38 ms.

Six atrial pacing sites were selected for pacing at a cycle length of 460 ms. The stimulus-delta intervals and the QRS duration from these sites were as follows: (1) High right atrium, with a stimulus-delta of 130 ms and QRS duration of 120 ms (Fig. 4A). (2) Low lateral right atrium, with a stimulus-delta of 140 ms and QRS duration of 120 ms. (3) Low septal right atrium, with a stimulus-delta of 100 ms and QRS duration of 100 ms (Fig. 4C). (4) Proximal coronary sinus, with a stimulus-delta of 60 ms and QRS duration of 140 ms (Fig. 4D). (5) Midcoronary sinus, with a stimulus-delta of 80 ms and QRS duration of 140 ms (Fig. 4E). (6) Distal coronary sinus with a stimulus-delta of 100 ms and QRS duration of 130 ms (Fig. 4F).

Retrograde atrial activation sequences were determined during ventricular pacing. The proximal coronary sinus atrial electrogram preceded the low septal right atrial, high right atrial, low lateral right atrial, and distal coronary sinus activation by 5, 20, 60, and 30 ms, respectively. The retrograde

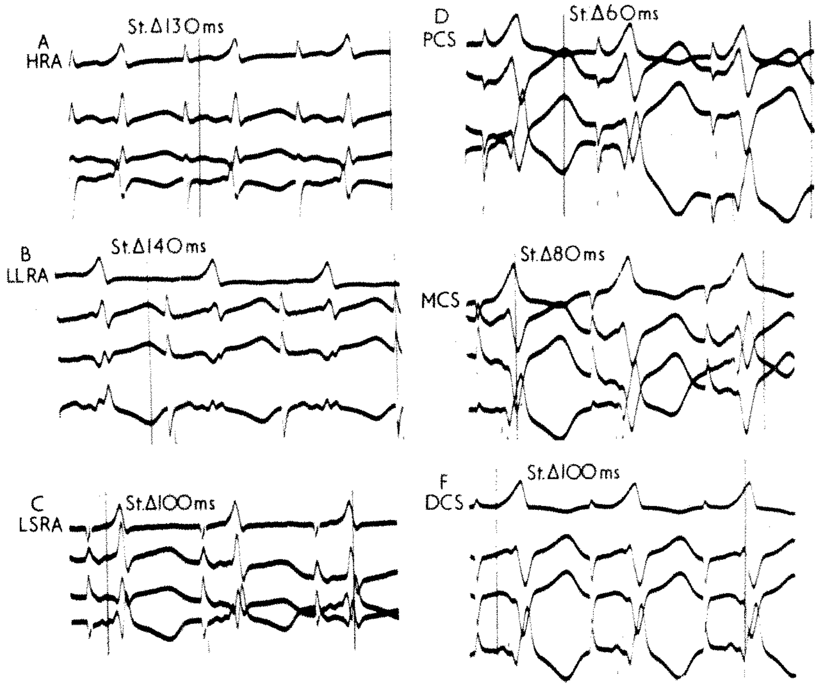

Fig. 4 *The effect of atrial pacing at multiple sites on stimulus-delta intervals in case 4 with type A pre-excitation. In each panel, surface electrocardiographic leads I, II, III, and V1 are shown. Abbreviations are similar to Fig. 1 and 3. PCS and MCS represent proximal and mid coronary sinus pacing. Note that the shortest stimulus-delta interval (60 ms) is obtained with proximal coronary sinus pacing.*

conduction time to the proximal coronary sinus site was 60 ms with ventricular pacing at all tested cycle lengths.

Comment

In this patient, the electrocardiogram suggested a left posterior connection. The atrial pacing site study revealed the shortest stimulus-delta and widest QRS complex from the proximal coronary sinus, suggesting a posterior left atrial connection. Though this anomalous pathway location was not confirmed with epicardial mapping and surgery, retrograde activation data provided strong confirmatory evidence for the predicted site of pre-excitation (Gallagher *et al.*, 1975).

CASE 5

This was a 53-year-old man with primary myocardial disease, subacute pericarditis, and recurrent paroxysmal atrial flutter with 1:1 anomalous pathway conduction. Electrocardiogram revealed type C pre-excitation (Fig. 5). Basic conduction intervals were recorded during sinus rhythm at a cycle length of 980 ms and revealed a P delta interval of 130 ms, and a PA of 25 ms. AH and HV intervals could not be measured since the H potential was buried within the ventricular electrogram.

Five stimulation sites were selected for pacing at a cycle length of 460 ms. The stimulus-delta intervals and QRS duration from these sites were as follows: (1) High right atrium, with a stimulus-delta of 170 ms and QRS duration of 180 ms (Fig. 5A). (2) Low lateral right atrium, with a stimulus-delta of 180 ms and QRS duration of 180 ms (Fig. 5B). (3) Low septal right atrium, with a stimulus-delta of 140 ms and a QRS duration of 140 ms (Fig. 5C). (4) Proximal coronary sinus, with a stimulus-delta of 80 ms and QRS duration of 190 ms (Fig. 5D). (5) Distal coronary sinus, with a stimulus-delta of 70 ms and QRS duration of 190 ms (Fig. 5E).

Because of pericarditis and medically intractable recurrent atrial flutter with hypotension necessitating frequent cardioversions, surgical ablation of the anomalous connection was attempted. After pericardectomy, the ventricular epicardium was mapped. The earliest area of ventricular activation was on the posterolateral left ventricle adjacent to the AV ring, preceding the onset of the delta wave by 25 ms (Fig. 6). After epicardial mapping, the left atrium was entered during cardiopulmonary bypass. A transmural atrial incision was made parallel to the AV ring and adjacent to the earliest site of ventricular activation, which resulted in normalisation of the electrocardiogram with loss of the delta wave. During surgical repair, the left circumflex artery was damaged with development of intraoperative myocardial infarction. The patient expired with postoperative cardiogenic shock.

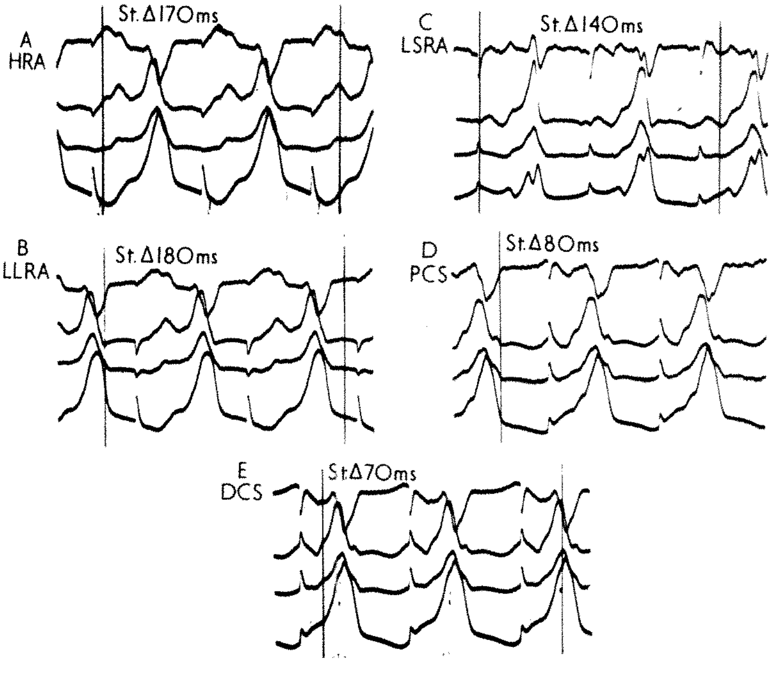

Fig. 5 *The effect of atrial pacing site on stimulus-delta intervals in case 5 with type C pre-excitation. In each panel, surface electrocardiographic leads I, II, III, and V1 are shown. Abbreviations are similar to Fig. 1 and 4. Note that the shortest stimulus-delta interval (70 ms) is obtained with distal coronary sinus pacing.*

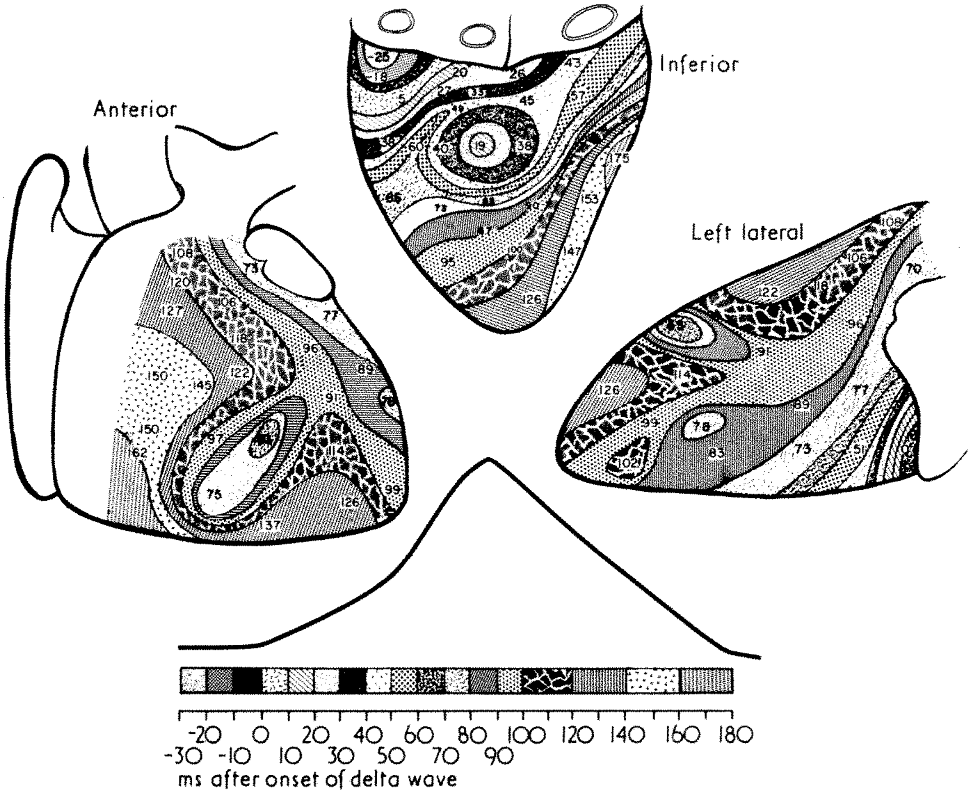

Fig. 6 *Diagram of epicardial activation in case 1 during pre-excitation. Isochronous lines are drawn at 10 to 20 ms intervals with reference to the earliest onset of delta wave on multiple surface electrocardiographic leads. Anterior (upper), left lateral (lower left), and inferior (lower right) views of the heart are shown. The earliest area of epicardial activity is on the anterior right ventricle preceding the onset of the delta wave by 38 ms.*

Comment

The electrocardiogram during total pre-excitation suggested a left lateral anomalous connection. Multiple pacing site study strongly suggested a left lateral bypass, because of the shortest stimulus-delta (70 ms) with distal coronary sinus pacing. Epicardial mapping and surgery confirmed the presence of a left lateral anomalous connection.

Discussion

The success of surgery in the Wolff-Parkinson-White syndrome is partially determined by anomalous pathway location. In a recent report by Tonkin *et al.* (1975) cure of pre-excitation was achieved in 91 per cent of patients with anomalous pathways located in the free wall of the mitral or tricuspid annulus. In contrast, cure of pre-excitation was achieved in only 36 per cent of cases with septal anomalous pathways (Tonkin *et al.*, 1975). Thus, the ability to predict the site of anomalous pathway before operation is of major importance in the presurgical evaluation of patients with pre-excitation.

Electrophysiological studies in the catheterisation laboratory may allow localisation of anomalous pathway location. The means for achieving this localisation are as follows: (1) Recording of retrograde atrial activation sequences from multiple sites during AV re-entrant tachycardia or ventricular pacing, (2) observations of changes in retrograde atrial activation time during the occurrence of functional bundle-branch block, allowing lateralisation of the anomalous pathway, and (3) measurement of stimulus-delta intervals and QRS duration from multiple atrial stimulation sites.

The use of retrograde atrial sequence and of functional bundle-branch block has been described in detail in recent publications (Coumel and Attuel, 1974; Spurrell *et al.*, 1974; Zipes *et al.*, 1974; Svenson *et al.*, 1974; Wellens and Durrer, 1974; Gallagher *et al.*, 1975; Neuss *et al.*, 1975; Tonkin *et al.*, 1975). The use of atrial stimulation at multiple sites has received less attention. Wellens *et al.* (1971) noted that left atrial pacing produced more pre-excitation than right atrial pacing in one patient with type A pre-excitation. Touboul *et al.* (1972) made similar observations in 2 patients with type A Wolff - Parkinson - White syndrome. Recently, Svenson *et al.* (1975) reported on the electrophysiological evaluation of 25 patients with Wolff-Parkinson-White syndrome and commented that the degree of ventricular pre-excitation was greatest and the stimulus-delta interval was shortest when atrial pacing was performed from the site at which earliest atrial activation was recorded during AV re-entrant tachycardia. However, the atrial sites tested and their stimulus-delta intervals were not reported.

The present study systematically presents multiple site data in 5 patients with the Wolff-Parkinson-White syndrome. In each of our cases, an atrial stimulation site with shortest stimulus-delta interval could be identified, as could a site with longest stimulus-delta. Several assumptions were made in evaluating our data. First, it was assumed that anomalous pathway conduction time was constant and independent of atrial stimulation during pre-excitation. Secondly, it was assumed that atrial conduction velocity was constant and independent of the site of atrial pacing. We did recognise that the anomalous pathway may respond in an all-or-none fashion depending upon the site of stimulation (Svenson *et al.*, 1975). Accepting these assumptions, differences in stimulus-delta intervals between different stimulation sites should reflect varying distances between atrial stimulation site and the atrial insertion of the anomalous pathway. The atrial pacing site with the shortest stimulus-delta interval should correspond to a location closest to the atrial insertion of the anomalous pathway. Conversely, the longest stimulus-delta interval should be obtained from the most distant atrial pacing site.

In the present study, the shortest observed stimulus-delta interval in each of the patients was between 60 and 80 ms. In all patients, the difference between shortest and longest stimulus-delta interval was always between 60 and 110 ms. The hypothesis that the site with shortest stimulus delta reflected the atrial insertion of the anomalous pathway appeared to be confirmed. In 3 of our patients, one each with right anterior, right posterior, and left lateral anomalous pathway locations, this confirmation was obtained by epicardial mapping and anomalous pathway surgery. In 2 of our patients, though epicardial maps were not obtained (surgery being avoided in these patients because of the results of pacing site studies), strong supportive evidence for the predicted site of pre-excitation was obtained by use of retrograde activation data. The latter technique has been previously confirmed to be of value in predicting anomalous pathway location with epicardial mapping (Svenson *et al.*, 1974, 1975; Gallagher *et al.*, 1975). It should also be pointed out that multiple stimulation site studies allowed differentiation of the site of anomalous pathways in patients with similar electrocardiographic findings.

CLINICAL IMPLICATIONS

The present study suggests that atrial pacing at multiple stimulation sites provides useful information in the electrophysiological assessment of patients with Wolff-Parkinson-White syndrome who are being considered for pre-excitation surgery. The demonstration of a stimulation site with shortest stimulus-delta interval, particularly if that interval is less than 80 ms, is strong evidence for that site being close to the atrial insertion of the anomalous pathway. The simultaneous demonstration of maximum pre-excitation at a relatively slow-paced rate from the same site provides additional supportive evidence. However, if normal pathway time is rapid from the site of the short stimulus delta, then maximum pre-excitation might not be noted (Amat-y-Leon *et al.*, 1975).

The use of multiple pacing site data appears to be particularly useful in detecting patients with septal anomalous pathways. In this group of patients, electrocardiograms do not reveal pathognomonic findings of septal pre-excitation, but usually suggest either left or right posterior pre-excitation (Tonkin *et al.*, 1975). Studies of retrograde conduction in these patients (either with ventricular pacing, or during paroxysmal tachycardia) show early activation of the low septal right atrium (Svenson *et al.*, 1975). Previous studies have shown that the normal sequence of retrograde atrial activation in patients without pre-excitation is characterised by earliest activation of the low right atrial septum (Amat-y-Leon *et al.*, 1976). This is also true in patients with AV nodal re-entrant paroxysmal tachycardia, when examining the activation sequence of AV nodal re-entrant atrial echo beats (Amat-y-Leon *et al.*, 1976). On theoretical grounds, one would also expect a similar retrograde activation pattern from a retrogradely conducting James tract (atrionodal connection) or atriofascicular tract (Anderson *et al.*, 1975). Thus, demonstration of early retrograde activation of low septal right atrium would not be pathognomonic of septal pre-excitation. Demonstration of the shortest stimulus-delta interval with low right atrial septal pacing would provide strong evidence for the presence of an anterogradely conducting septal anomalous pathway bypassing the AV node.

The present study thus indicates that atrial pacing at multiple sites is useful in the evaluation of patients with Wolff-Parkinson-White syndrome, and supplements the other methods used for prediction of site of pre-excitation. The use of atrial sites provides relatively direct information concerning the location of anterogradely conducting anomalous pathways.

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Endocardial pacing electrode design and rate of displacement

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In a series of 184 patients with a permanent endocardial pacing system the rate of electrode displacement was 3·0 per cent using the Devices L120 SR electrode, and 23·1 per cent using the Devices S120 electrode. The technique and pacing team were unchanged during the period of study. It is suggested that the design and mechanical characteristics of the electrodes were responsible.

The safety and convenience of the transvenous approach to long-term endocardial pacing are well established, but its principal drawback is electrode displacement (Goldstein *et al.*, 1970). The reported incidence of this complication varies from 0 to 44 per cent (Parsonnet, 1970; Morse *et al.*, 1973; Bette *et al.*, 1975; Fiandra *et al.*, 1976) and is highest in the early post-implantation period before endocardial fixation of the electrode tip. The Inter-Society Commission for Heart Disease Resources report on pacemakers (Parsonnet *et al.*, 1974) suggests that a rate of early displacement greater than 5 per cent calls for a critical review of results. Variations in displacement rate may accompany changes in the technique of electrode insertion (Simmons *et al.*, 1970) and in the experience of the operators involved (Goldstein *et al.*, 1970). In the present series a sharp increase in displacement rate accompanied a change in the type of electrode used. The same experienced operators used a standard technique throughout the period of study.

Subjects and methods

PATIENTS

From July 1974 to April 1976, 184 patients were equipped with permanent endocardial pacing systems. In 132 patients the Devices L120 SR electrode was used, and in 52 patients the Devices S120 electrode.

PROCEDURE

Electrodes were inserted by the infraclavicular subclavian approach and manipulated into the apex of the right ventricle under fluoroscopic control. The suitability of the position was confirmed by attaining an endocardial potential of 5 millivolts or more, and a pacing threshold of less than 1 volt. The electrode was anchored by a silk or linen tie at the point of entry, and a loop made using silicone rubber twin tubing. The electrode was secured in the distal limb of the tubing, and the latter anchored to the deep fascia. The generator was implanted in the pectoral region and the patient was kept in hospital for 4 days.

ELECTRODES

From July 1974 to October 1975, the Devices L120 SR electrode was used. This comprises a quadruple helical wound lead wire insulated by polythene with a short silicone rubber sleeve just proximal to the electrode tip. From November 1975 to April 1976 the Devices S120 electrode was substituted. The lead wire is wound as a single helix and is insulated with silicone rubber. There is no sleeve at the tip.

Results

The incidence of electrode displacement is shown in the Table. Early displacement is defined as within the first month after insertion, and late displacement as that occurring later than one month.

Table *Incidence of electrode displacement*

		L120 SR	*S120*
No. of patients		132	52
No. of displacements	Early	0	7
	Late	4	5
Overall percentage displacement		3·0	23·1

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Discussion

Electrode durability is becoming an increasingly important factor in long-term pacing. In this department the decision to change to S120 electrodes was taken because silicone rubber insulation is possibly more resistant to mechanical stress and to the action of body fluids than the polythene insulation of the L120 SR. However, the change in policy was attended by an eightfold increase in electrode displacement, all other factors remaining constant.

There are two possible causes, both related to electrode design. Firstly, the polythene insulated quadruple wound L120 SR electrode is stiffer and more damped and consequently has greater resistance to lateral movement. The silicone rubber insulated S120 electrode is more flexible and, therefore, tends to spring back to a straight position more readily if deviated to one side or the other. Secondly, the L120 SR electrode has a short segment of sleeving over the insulation near the electrode tip which helps to trap the tip among the ventricular trabeculae; the S120 electrode is without this feature. It is suggested that these factors may account for the higher displacement rate of the S120 electrode, 9 of which occurred in the first 6 weeks after insertion before effective anchoring to the endocardium by fibrosis (Goldstein *et al.*, 1970).

The technique for electrode placement in the right ventricle was unchanged in this series. With the stiffer L120 SR electrode a satisfactory electrical position in the right ventricle is relatively easily obtained, and though an effort was made in all cases to place the electrode as peripherally as possible in the right ventricle, a less peripheral position was sometimes accepted provided that the other parameters were satisfactory.

It may be argued that in using a less stiff electrode such as the S120, greater care needs to be exercised in its placement and that better stability may be achieved by ensuring that it is lodged more peripherally in the right ventricle. Though this is not entirely discounted by our experience, we do not think that this factor played an important part in our high displacement rate. In the majority of our patients, including those who experienced displacement, the electrode as gauged from anteroposterior and lateral radiological projections was wedged peripherally in the apex of the right ventricle, in a position that was entirely acceptable.

An unacceptably high displacement rate with the S120 electrode has been encountered by at least one other cardiac department using an implantation technique similar to ours (E. B. Raftery, 1976, personal communication).

It is concluded that a relatively damped wire, and a barbed or flanged electrode tip are desirable features of an electrode lead system for permanent endocardial pacing.

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Non-invasive recording of mitral valve flow velocity patterns using pulsed Doppler echocardiography

Application to diagnosis and evaluation of mitral valve disease[1]

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A new technique using pulsed Doppler echocardiography for non-invasive recording of blood flow velocity patterns at the site of the mitral annulus is described. In a control group of 30 subjects in whom an organic or functional lesion of the mitral valve had been ruled out, the normal flow velocity pattern was found to be similar to that obtained either experimentally by other authors using an implanted electromagnetic cuff flowmeter or clinically by our group using the transseptal catheterisation continuous wave Doppler technique. In 31 patients with confirmed mitral valve disease, the mitral valve flow velocity patterns were correlated with the clinical and haemodynamic data, and in 10 cases the patterns were compared with the flow velocity curves recorded in the same patients using the Doppler ultrasonic transseptal catheterisation of the mitral valve. In most cases, characteristic anomalies of these patterns were noted and could be related to the type of the lesion, stenosis, regurgitation, or a combination of these.

Specific patterns of mitral valve flow velocity profiles were shown to correlate satisfactorily with the degree of the lesion, with some reservations for mitral regurgitation. Though not fully quantitative, the pulsed Doppler technique is a new and promising non-invasive method for establishing the diagnosis of mitral stenosis and/or regurgitation, and to some extent, grading the severity of mitral valve disease using pattern recognition. It provides an original approach to the understanding of mitral haemodynamic disturbances on a beat-to-beat basis.

The paramount importance of the knowledge of instantaneous transmitral blood flow for our understanding of/and our ability to diagnose accurately mitral valve disease has been recently stressed (Kalmanson, 1976). We have previously shown the diagnostic use of continuous wave Doppler ultrasonic transseptal catheterisation of the mitral valve for such purposes (Kalmanson *et al.*, 1975a, b). Unfortunately, the cumbersome and traumatic nature of such a procedure somewhat restricts its routine application in clinical cardiology and therefore led us to search for a non-invasive technique for investigating mitral valve flow.

In 1973, Baker (Johnson *et al.*, 1973) devised a new technique for localising the origin of heart murmurs by demonstrating the sites of turbulent blood flow using the combined transcutaneous pulsed Doppler and conventional echocardiographic procedures. At our request, the audio frequency output signal of the pulsed Doppler was demodulated by means of a frequency-to-voltage converter and a single continuous curve was thus substituted for the frequency spectral display previously necessary to interpret the output signal. A new method was devised and tested by our group for recording blood flow velocity patterns from the heart valves. The encouraging results are presented here.

Subjects and methods

We first studied a control group of 30 subjects, 13 women and 17 men, ranging in age from 7 to 40 years, all with normal hearts or in whom organic or

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Table 1 *Haemodynamic data of patients with pure mitral stenosis*

Case No.	*Rhythm*	*LA pressure (mmHg)*		*LV pressure (mmHg)*			*Measured or calculated pressure gradient (mmHg)*	*RA pressure (mmHg)*		*RV pressure (mmHg)*			*PA pressure (mmHg)*		*Cap pressure (mmHg)*	
		S/D	*Mean*	*S/D*	*ED*	*Mean*			*Mean*			*Mean*		*Mean*		*Mean*
1	SR	16/6	13	94/0	6	40	18	2/–2	0	34/–2	2	14	34/15	23	23/12	17
2	AF						2	4/–1	2	20/–1	2	7	20/8	14		7
3	SR						7	8/3	5	30/0	5	10	28/10	18		12
4	SR	12/5	[illegible]	97/–2	4	34	4	4/1	2	23/0	3	8	20/10	13		7
5	SR						21	3/–1	0	43/0	4	14	48/20	32	28/20	26
6	SR			115/2	12	44	7						22/12	18		12
7	SR						6	6/1	3	28/0	3	10	25/10	15	16/8	11
8	AF	34/18	23	104/–4	8	40	16			50/0	15	25	50/22	32	28/20	24
9	SR						5	7/3	5	27/3	7	17	27/10	16	14/8	10
10	SR	18/6	3	125/2	6	50	9			32/0	2	9	32/8	15		9
11	SR						7	5/0	2	27/0	4	16	27/12	18	20/9	12
12	SR	12/3	5	138/0	10	44	1·5	6/3	4	30/0	5	14	27/10	15		7
13	AF	7/5	3	200/0	5	68	3·5	5/1	2	28/0	1	11	30/8	19		9
14	SR	12/5	3	120/0	10	50	6·5	5/0	3	35/0	5	14	35/11	20		9
15	AF	30/14	23	157/–4	2	44	22	5/–2	0	38/–3	0	13	38/14	28		22
16	AF						10	4/0	3	30/0	2	14	30/15	21	20/13	15

LA, left atrium; S/D, systolic/diastolic; LV, left ventricle; RA, right atrium; PA, pulmonary artery; Cap, capillary; CI, cardiac index; MS, mitral stenosis; AS, aortic stenosis; AR, aortic regurgitation; SH, systemic hypertension; SR, sinus rhythm; AF, atrial fibrillation.

Table 2 *Haemodynamic data of patients with pure mitral regurgitation*

Case No.	*Rhythm*	*LA or cap pressure (mmHg)*			*LV pressure (mmHg)*			*CI ($l m^{-1} m^{-2}$)*	*Volume of regurgitation (% of CO)*	*Angiography*	*MR grading*	*Associated lesions*	*Surgery*
		S/D	*'v' wave*	*Mean*			*Mean*						
17	AF	8/4	16	8	112/6	7	48	2·1	50		3		
18	SR	7/1 cap	8	5	114/0	4	46	3·7	10	Anomalous antr MV kinetics	1		
19	AF							2·4	15		2	My inf	
20	AF	12/8	30	17	130/2	10	44	3·9	20		2		
21	SR	14/12	36	20	104/4	15	40	2·3	18		2	My inf	+
22	SR				120/0	5	38	/	/	Antr MV prolapse	1		
23	SR	19/5	52	20	100/0	12	36	1·6	25		3		
24	AF	12/10 cap	45	48	105/2	6	30	1·5	30	+	3		+
25	SR				140/–1	10	46	/	/	Postr MV prolapse	1		

For other abbreviations, see Table 1. MV, mitral valve; My inf, myocardial infarct.

Table 3 *Haemodynamic data of (catheterised) patients with associated mitral stenosis and regurgitation*

Case No.	*Rhythm*	*LA pressure (mmHg)*			*LV pressure (mmHg)*			*LA-LV pressure (mmHg)*	*CI ($l m^{-1} m^{-2}$)*	*Volume of regurgitation (% of CO)*	*Calculated mitral area (cm²)*	*MS grading*	*MR grading*	*Associated lesions*
		S/D	*'v' wave*	*Mean*	S/D		*Mean*							
26	AF	20/18	20	22	100/0	5	39	17	2·0	20	1·0	3	2	TR+PH
27	SR	13/5	10	12	114/0	4	40	5	2·6	10	1·8	2	1	AS
28	SR	12/5	10	8	110/0	4	36	5	2·7	5	1·8	2	1	
29	SR	14/2	9	8	80/0	5	40	6	3·3	10	1·5	2	1	
30	SR	21/15	30	20	88/0	6	38	16	2·3	20	1·1	3	3	PH
31	SR	12/8	15	10	130/–4	10	40	6·7	1·9	10	1·0	3	1	TR

For other abbreviations, see Table 1. TR, tricuspid regurgitation; PH, pulmonary hypertension.

CI *(l m^{-1} m^{-2})*	*Calculated mitral area (cm^2)*	*MS grading*	*Associated lesions*	*Surgery*
3	1·2	3		
2·1	2·2	1		
3·5	2·0	1		
2·7	2·3	1		
2·8	0·7	3		+
3·7	2	1		
2·6	0·9	3		+
3·5	1·7	2	AS + AR	+
2·1	1·6	2		
2·8	1·5	2		
3·0	1·8	2	AR	
2·5	3	1		
2·0	2·5	1	SH	
3·7	1·7	2	AR	
2·0	0·6	3		
1·88	1·0	3		

functional mitral valve disease was excluded by classical investigation procedures.

Thirty-one patients were studied, 21 women and 10 men, ranging in age from 23 to 71 years (Tables 1, 2, and 3). They included 16 patients with pure mitral stenosis, 9 with pure mitral regurgitation, 6 with associated mitral stenosis and regurgitation. The mitral stenosis was all of rheumatic origin. The aetiology of the mitral regurgitation included rheumatic heart disease (3), papillary muscle dysfunction (2), prolapse of the mitral valve (3), floppy valve (1); 6 had associated aortic and/or tricuspid valve lesions; 21 were in sinus rhythm, and 10 in atrial fibrillation. All patients but 2 underwent either a left or a right heart catheterisation, or both using a Telco manometer.[1] In addition, 10 patients had a continuous wave Doppler transseptal catheterisation in order to determine the ultrasonic mitral valve flow velocity pattern using the directional Sonicaid Doppler (Sonicaid BV 180) catheter-tip velocimeter, using a previously described technique (Kalmanson *et al.*, 1975a).

Cardiac output was measured by the dye (indocyanine green) dilution technique using the Waters[2] apparatus. Mitral valve area was calculated using the Gorlin formula with correction for any mitral regurgitation which was assessed by dye dilution and/or left ventriculography.

CLASSIFICATION OF PATIENTS

We used 4 grades of severity: (0, no lesion; 1, mild; 2, moderate; 3, severe). The classification of

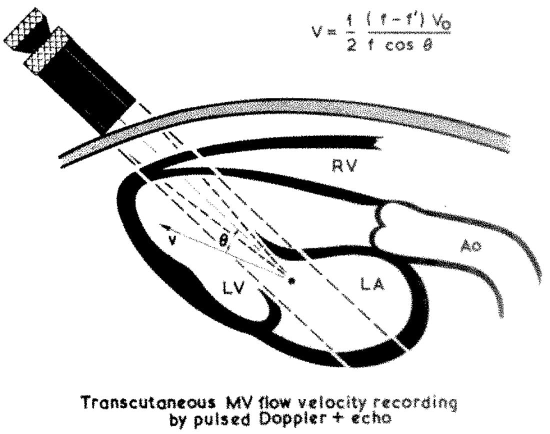
$V = \frac{1}{2}\frac{(f-f')V_0}{f\cos\theta}$
RV
Ao
v
θ
LV
LA
Transcutaneous MV flow velocity recording
by pulsed Doppler + echo

Fig. 1 *The ultrasonic pulsed beam is backscattered (a) from the cardiac structures and displayed in the M-mode on the oscilloscope; (b) from a small sample of blood at the annulus according to the Doppler principle. Orientation of the beam towards a direction parallel to the inflow of blood into the left ventricle (v) is crucial in order to minimise the incidence of the unknown angle θ and obtain a good 'Doppler' audible signal.*

the pure or predominant lesion on this four-point scale was based partly on the severity of the symptoms, and partly on the clinical presentation (bedside examination, *x*-ray, electrocardiogram, and clinical course) as well as on the haemodynamic data. For mitral stenosis, grading was based on the left atrial to left ventricular pressure gradient and particularly on the calculated mitral area: greater than 1·8 cm^2 for grade 1, from 1·8 to 1·3 cm^2 for grade 2, and less than 1·3 cm^2 for grade 3; it was appreciated that borderline cases might occasionally overlap these categories. For mitral regurgitation grading was based on a large atrial 'v' wave, dye dilution curves, and/or angiocardiography, and for both lesions, surgical findings, when appropriate. Lesions associated with those of the mitral valve were also classified in 4 grades depending on the clinical and haemodynamic data, and surgical findings. The haemodynamic data are summarised in the Tables.

TECHNIQUE

The range-gated ultrasonic pulsed Doppler technique has been described elsewhere (Baker, 1970; Peronneau *et al.*, 1970). The principle, the apparatus, and use of Doppler combined with echocardiography using a spectral analyser has also been described (Johnson *et al.*, 1973). Here it is, therefore, only necessary to emphasise the essential characteristics and the modifications caused by the use of an analogue readout (Fig. 1).

[1] Thomson-Telco, 92212 Saint-Cloud, France.
[2] Waters, Rochester, Minnesota, U.S.A.

(a) *The Doppler principle*

The instantaneous flow velocity of a small (2×4 mm) tear-drop shaped sample volume of blood is proportional to the frequency shift between ultrasonic beams emitted to, and back-scattered from, the red blood cells of the sample (Fig. 1). A range gating system makes it possible to pick up any desired sample of blood along the axis of the ultrasonic beam within the depth limitations (5 to 17 cm).

(b) *Apparatus*

We used the ATL[1] blood flow meter 500A with an analogue readout. The small (0·6 cm diameter) disc-shaped piezoelectric crystal transmits brief pulses (1·0 to 1·5 μs) of high frequency ultrasound (3·0 MHz), at a pulse repetition rate ranging from 2 to 15 KHz. The output wave form is a spectrum of frequencies but can be transformed into a curve by an analogue converter whose readout may be recorded on a strip chart. The use of a zero-crossing detector for obtaining an analogue readout unquestionably underestimates the true value of flow velocity in highly turbulent flow, which is always present in mitral stenosis and most often in mitral regurgitation. It is, therefore, worth emphasising that the method presently proposed relies exclusively *on pattern recognition* and not on accurate measurements of absolute velocities as will be subsequently shown, but this drawback does not affect in the least the diagnostic value of our method. The Doppler signal can also be fed to a loud speaker. The apparatus includes a conventional

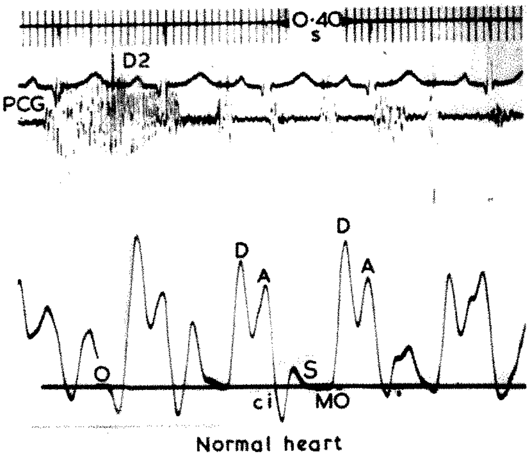

Fig. 2 *Normal flow velocity pattern. From top to bottom: Lead II of electrocardiogram, phonocardiogram at the second left interspace, flow velocity trace. Distance between small vertical bars equals: 0·04 s. The systolic curve begins with a brief negative deflection (ci) caused by the isometric contraction of the left ventricle, thereafter the curve rises abruptly, and follows closely the baseline during the remainder of systole. During diastole, the curve rises sharply and presents two successive triangular-shaped waves. D, initial filling wave; A, atrial contraction wave; MO, point of true mitral opening.*

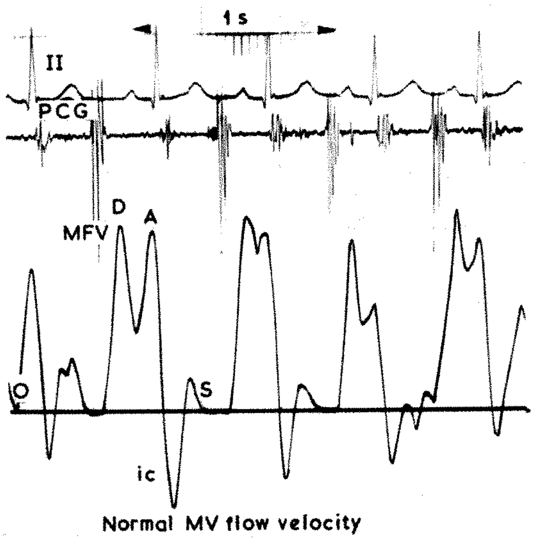

Fig. 3 *Normal mitral flow velocity patterns. Depending on the length of the RR interval, the D and A waves may become more or less fused.*

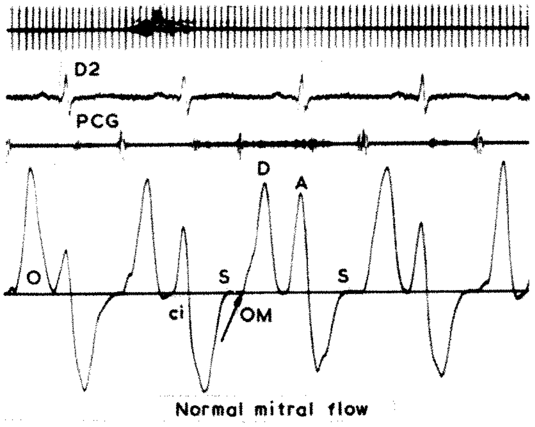

Fig. 4 *Normal mitral flow pattern. After the negative deflection at the beginning of systole, the curve became upright, with a small delay probably caused by an artefact. Such an initial negative wave should not be mistaken for a mitral regurgitation wave. Note that in Fig. 2, 3, or 4 there is no intermediate segment elicited between the normal D and A waves.*

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[1] ATL, Bellevue, Washington, U.S.A.

echocardiograph with two oscilloscopes (A and M mode). A single transducer operates simultaneously both for the Doppler and the echocardiographic procedures (Fig. 1). The location of the Doppler gate can be displaced using a knob and monitored on the scopes. The approximate time delay determined by comparison with an electromagnetic flowmeter was 65 ms ±10 per cent. It may be considered that the device is linear within 5 per cent within the range from 0 to 100 cm/s for steady flow.

(c) *Recording technique*

In the first place, the transducer coated with conductive jelly is placed on the skin near the fourth left intercostal space of the reclining patient, and is used, according to the conventional echo-technique, to obtain the mitral valve anterior leaflet and the annulus on both scopes. Thereafter, and in contrast to the previously described echo-Doppler technique for localising heart murmurs, the transducer is moved towards the apex, and its direction is modified in order to orientate the ultrasonic beam parallel to the axis of the mitral annulus which turns out to approximate to the anatomical apex-base axis of the heart. The operator must then make the gate coincide with the site of the mitral annulus. The correct orientation is ascertained when a typical Doppler sound is heard, which indicates that the ultrasonic beam is nearly parallel to blood flow. For each patient, it is possible by modifying the location and orientation of the transducer and/or that of the gate to explore several points of the mitral annulus, including the centre, the commissural areas, and the intermediate regions. Failure to explore carefully the mitral annulus may lead to a lesion being overlooked or its severity being underestimated. It is also necessary to take records at various times in the respiratory cycle, and with the breath held.

(d) *Recordings*

The traces were recorded in apnoea or very quiet respiration, with the patients lying on their backs or in the left lateral position, and were inscribed on an 8-channel photographic Irex[1] recorder, simultaneously with lead II of the electrocardiogram and frequency selecting phonocardiogram. Chart speed was 50 mm/s, unless otherwise specified. The distance between two successive vertical bars equals 40 ms.

Results

The recorded curves represent the velocity patterns at different points of the mitral annulus. Since the device is directional, a positive or negative sign of velocities depends on the orientation of the transducer with respect to the direction of blood flow.

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[1] Irex, Mahwah, New Jersey, U.S.A.

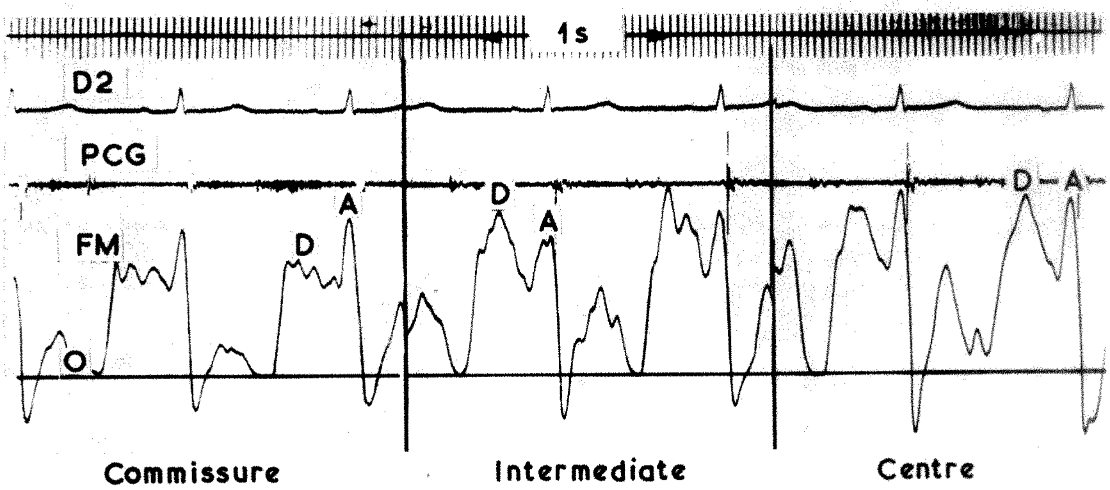

Fig. 5 *Mitral flow velocity patterns in pure mild stenosis with sinus rhythm. Right: recording at the centre of the orifice, the D wave is normal, and discloses no indentations. Middle: intermediate region, some small indentations appear either late on the ascending limb of the D wave which retains a normal slope, or at the beginning of its descending limb. Left: recording at the commissure, the summit of the D wave is cut off and replaced by a jagged plateau. Note the absence of any abnormal negative wave throughout the different tracings. Case 12, calculated mitral area: 3 cm²*

By convention, positive velocities apply to blood flowing from the left atrium into the left ventricle. Negative velocities apply to blood regurgitating from the left ventricle into the left atrium and also to atrial blood pushed back by an upward displacement of a closed and competent mitral valve.

NORMAL PATTERN OF MITRAL VALVE FLOW VELOCITY (Fig. 2, 3, and 4)

In normal subjects, the curve starts at the beginning of systole with a large precipitous and brief negative deflection (0·05 to 0·08 s), labelled ci, closely related to the first vibrations of the first heart sound. Then the trace rises more or less rapidly, rejoins the zero line, and keeps close to the latter throughout the remainder of systole. It often shows a small angulation related to the aortic component of the second heart sound, followed by a short positive, diaphasic, or negative segment, ended by a clear-cut inflection point (0). Thereafter, the diastolic part of the curve shows two conspicuous, positive (forward flow) waves: the first early and mid-diastolic, labelled D, starting shortly after the aortic component of the second heart sound, triangular in shape, with a peak occurring (depending on the heart rate) from 0·13 to 0·20 s after the second sound. It is followed by an end-diastolic wave, labelled A, also triangular in shape, starting from 0·10 to 0·12 s, and reaching a peak from 0·16 to 0·20 s after the onset of the P wave. Peak velocities of the D and A waves vary inversely, depending on heart rate and respiration. For normal or slow rates the D wave is larger than the A wave and inversely for faster rates. In cases with long PR intervals (equal to or greater than 0·20 s), the descending limb of the A wave falls precipitously and overrides the zero line before the occurrence of the first heart sound.

Other patterns, showing small variations, can be elicited, depending on the site of the recording. The negative initial ci deflection may be absent, or sometimes prolonged for a short period of early systole (Fig. 4). In subjects with a heart rate above 60/min, never more than two filling waves were recorded, whereas in subjects with a slower heart rate, an intermediate segment, usually in the form of a small bulge, occurred between the initial D and the end-diastolic A waves.

PATIENTS WITH MITRAL VALVE DISEASE

Pure mitral stenosis (16 cases)

In all patients, the diastolic part of the curves consistently showed anomalies of the D wave, of various patterns, depending on the severity of the lesion and on the site of the recording with respect to the centre and the commissural areas.

Mild stenosis (Fig. 5) (6 patients) At the centre of the annulus a normal pattern was consistently recorded, including a smooth D wave of normal timing and amplitude. When moving from the centre toward the commissures, small indentations

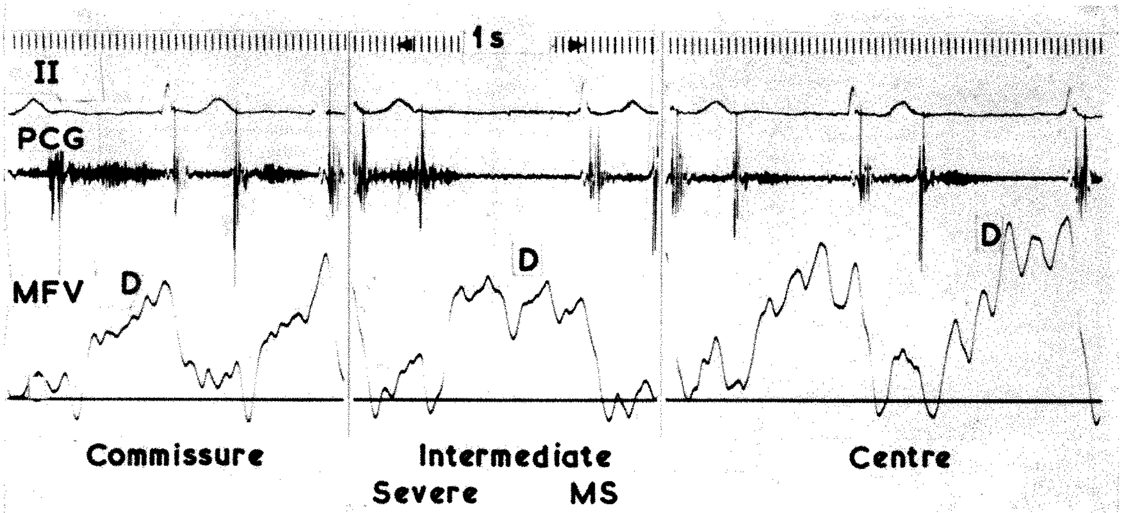

Fig. 6 *Mitral flow velocity patterns in severe pure stenosis with atrial fibrillation. At no point can a normal pattern be elicited. All tracings show a cut-off, serrated, either plateau-like or ascending D wave. Case 15, calculated mitral area: 0·6 cm².*

occurred, late on the ascending limb, at the summit or even on the descending limb of the D wave. Noticeable anomalies were recorded only at the commissures, in the form of coarse indentations of most of the D wave, whose summit was cut off and lowered. In 3 patients, a conspicuous notch encroached on the ascending limb of the D wave approximately 65 ms after the occurrence of an opening snap recorded on the phonocardiogram. In the patients with atrial fibrillation, the same modifications were observed, save for the absence of the A wave.

Severe stenosis (Fig. 6 and 7) (5 patients) In all patients the velocity patterns were conspicuously distorted, showing at all sites early and coarse indentations of the D wave. At the commissural areas, the D wave was noticeably decreased in amplitude, with an ascending limb having a smaller slope than normal; the peak was either cut off and replaced by a serrated plateau or conspicuously delayed. The A wave was usually higher than the D wave (Fig. 7). At the centre the pattern was equally distorted, but the velocities tended to be larger, with an A wave of increased amplitude.

Moderate stenosis (4 patients) Patterns intermediate between the two previous ones were found consistently. The normal pattern could never be elicited, even at the centre. However, the overall velocities tended to be larger, the indentations occurred later, and were smaller than in patients with severe stenosis.

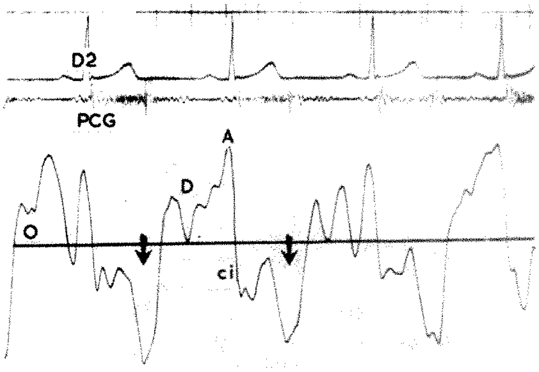

Fig. 8 *Flow velocity pattern in mild pure regurgitation. Case 25 with mitral valve prolapse and regurgitation less than 10 per cent of cardiac output. Note the brief and conspicuous reversal flow wave at the end of systole. The diastolic part of the curve is depressed because of the difference in spatial direction of the filling wave and of the regurgitating jet confirmed by angiography.*

Pure mitral regurgitation (9 patients)
Mild regurgitation (3 patients) The normal systolic S wave was replaced by a small negative wave, in one case prevailing at end systole (Fig. 8). The diastolic pattern remained normal or was decreased.

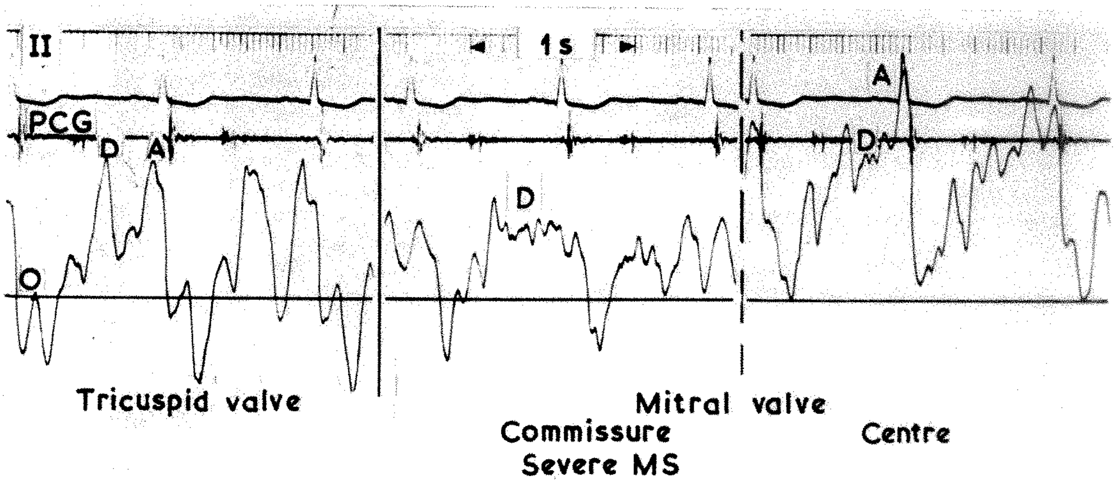

Fig. 7 *Mitral flow velocity patterns in severe pure stenosis with sinus rhythm. Compare the normal aspect of the flow velocity recorded at the tricuspid annulus (left) with those obtained at the centre (right) or at the commissures (middle). At the centre, the D wave is replaced by an irregular, sawtooth-like ascending segment, and at the commissure it is cut off and presents a jagged plateau. There is no abnormal negative wave during systole. Case 5, calculated mitral area: 0·7 cm²*.

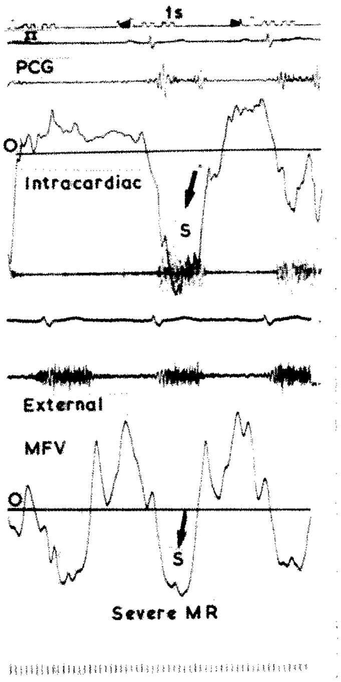

Fig. 9 *Flow velocity pattern in case of major regurgitation. Comparison with curve recorded by cardiac catheterisation. Lower row: transcutaneous recording. The systolic wave is replaced by a deep negative wave. Note the similarity of this systolic pattern with that of the curve recorded in the same patient during Doppler transseptal catheterisation of the mitral valve (upper row). Case 23, regurgitation: 30 per cent of cardiac output.*

Severe regurgitation (3 patients) In these cases, we consistently found a large amplitude, broad, negative systolic wave. Diastolic pattern was either normal or decreased and irregular. In 2 of these patients, who also underwent a velocimetric continuous wave Doppler transseptal catheterisation (Fig. 9), the externally recorded negative systolic wave pattern was consistently found to be strikingly similar to that of the intracardiac catheterisation curve.

Moderate regurgitation (3 patients) In these patients, a negative systolic wave of intermediate size was recorded, with a normal diastolic pattern.

Associated mitral stenosis and regurgitation (6 patients)

Mild or moderate stenosis and mild regurgitation (3 patients) A negative systolic S wave of small amplitude at one or several points of the annulus, or of moderate amplitude in the centre, was consistently associated with typical anomalies of the D wave found in the patients with mild or moderate stenosis (Fig. 10 and 11).

Severe stenosis and mild to moderate regurgitation (2 patients) Early and coarse irregular indentations of the D wave were associated with a negative systolic wave of small to moderate amplitude, usually at limited points, most often in the centre (Fig. 12). In 3 patients in whom the cardiac catheterisation did not disclose any regurgitation, we noted an associated small negative systolic either at the centre or at the commissure.

In this group of patients, the velocimetric continuous wave Doppler transseptal catheterisation, whenever available, disclosed a strikingly similar pattern for both diastolic and systolic anomalies (Fig. 12).

Severe mitral stenosis with important regurgitation (1 patient) Early beginning and coarse indentations of the D wave at all points of the annulus were associated at one or several points with a negative systolic wave of large amplitude (Fig. 13).

In 3 other patients (cases 1, 8, and 14), in whom the conventional procedures did not disclose any regurgitation, the pulsed Doppler showed a minute (2 cases) to moderate (1 case) negative systolic wave.

Discussion

It has been shown previously that particular anomalies of the mitral valve flow velocity curves recorded by continuous wave Doppler transseptal catheterisation correlated well both with diagnosis and assessment of severity of mitral valve disease. The present study leads to a similar conclusion—with the considerable advantage of now using a non-invasive approach. Both approaches raise many common problems, already discussed at length when dealing with the continuous wave Doppler technique, and, therefore, will not be considered here (Kalmanson *et al.*, 1969, 1972, 1975a, b). They include the following:

(1) The application of the Doppler principle to backscattered ultrasound from red blood cells for the measurements of instantaneous blood flow velocities. It is worth mentioning that accurate calibration of the velocity curves would require knowledge of the angle θ and an infallible frequency-to-voltage converter. In the present state of the art, it is impossible to make quantitative measurements. This shortcoming by no means affects the diagnostic value of the technique which is based on a pattern recognition method.

Incidentally, it is also interesting that the direc-

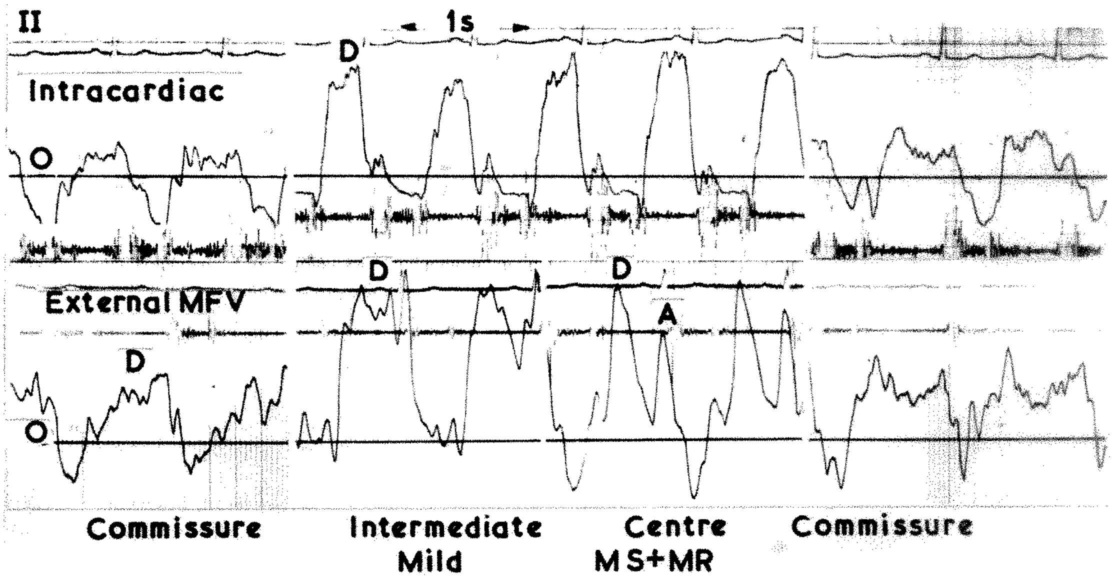

Fig. 10. *Mitral flow velocity pattern in moderate stenosis associated with mild regurgitation with sinus rhythm. Comparison with curves recorded in same patient by cardiac Doppler catheterisation (or with intracardiac curves). Upper row: curves recorded by transseptal catheterisation of the mitral annulus. Lower row: transcutaneous recordings. The curves recorded transcutaneously at the centre are normal during diastole and present in particular a normal smooth D wave of normal height. Near the centre, the D wave has still a normal amplitude but discloses late indentations. At the commissures, the D wave is erased and replaced by coarse identations. Note the striking similarity between corresponding curves of both rows, except for the normal pattern which could not be elicited during cardiac catheterisation. At the commissure, there is a small negative systolic wave. Case 14, calculated mitral area: 1·7 cm², insignificant regurgitation.*

tion of the left ventricular filling waves, that is that of the main axis of the mitral annulus, tends to parallel the anatomical apex-base axis of the heart (Henry *et al.*, 1959), a situation that minimised the role of the angle θ.

(2) Problems raised by Doppler echoes back-scattered from cardiac structures. In the pulsed Doppler technique these echoes can easily be detected, not only by the particular harsh Doppler

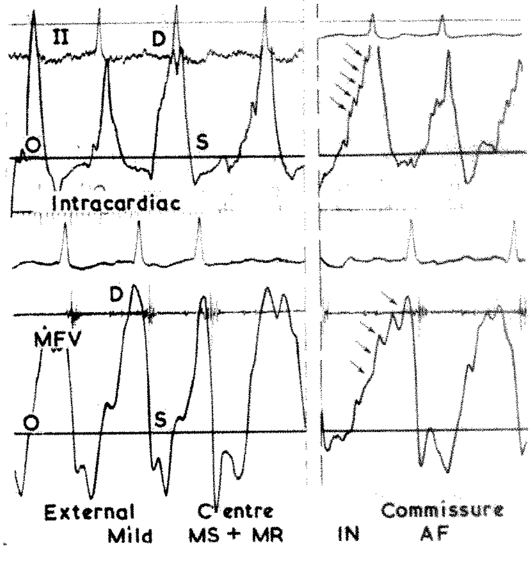

Fig. 11 *Mitral flow velocity patterns in mild stenosis with minute regurgitation with atrial fibrillation. Upper row: curves recorded by cardiac Doppler catheterisation. Lower row: transcutaneously recorded curves. Left: at the centre in both tracings, the D wave is of normal, large amplitude and smooth, without indentations. Right: at one commissure, both tracings show small indentations. Note the similarity between the intracardiac and transcutaneous patterns. Case 8, mitral calculated area: 1·7 cm², insignificant regurgitation.*

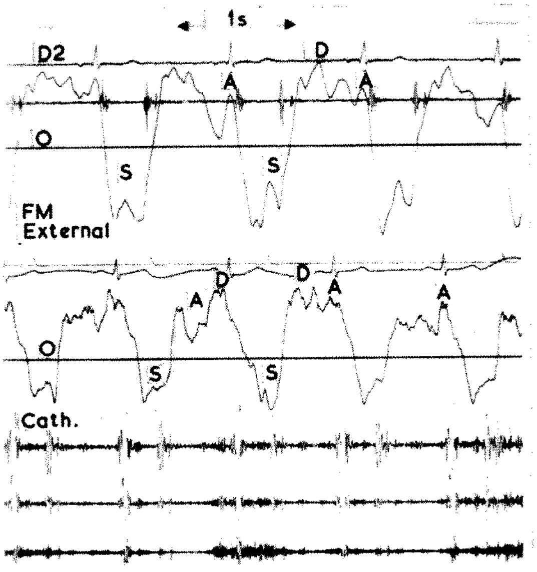

Fig. 12 *Mitral flow velocity patterns in severe stenosis with mild regurgitation. Upper row: transcutaneously recorded curves. Tracings recorded at the centre of the annulus (upper row: transcutaneously; lower row: using transseptal catheterisation). In both tracings the summit of the D wave is replaced by an irregular sawtooth-like plateau, whereas the systolic part of the curve shows a negative wave of small amplitude. Case 31, calculated mitral area: 1·0 cm², insignificant regurgitation.*

sound they generate, but also by the coincidence of the conventional echoes of these structures with the gate, displayed on the oscilloscopes.

The discussion here will, therefore, be limited to the physiological significance of the recorded curves.

VALIDITY AND SIGNIFICANCE OF RECORDED CURVES

The most important feature of the recorded patterns is their remarkable consistency with mitral valve flow volume or velocity tracings obtained by other

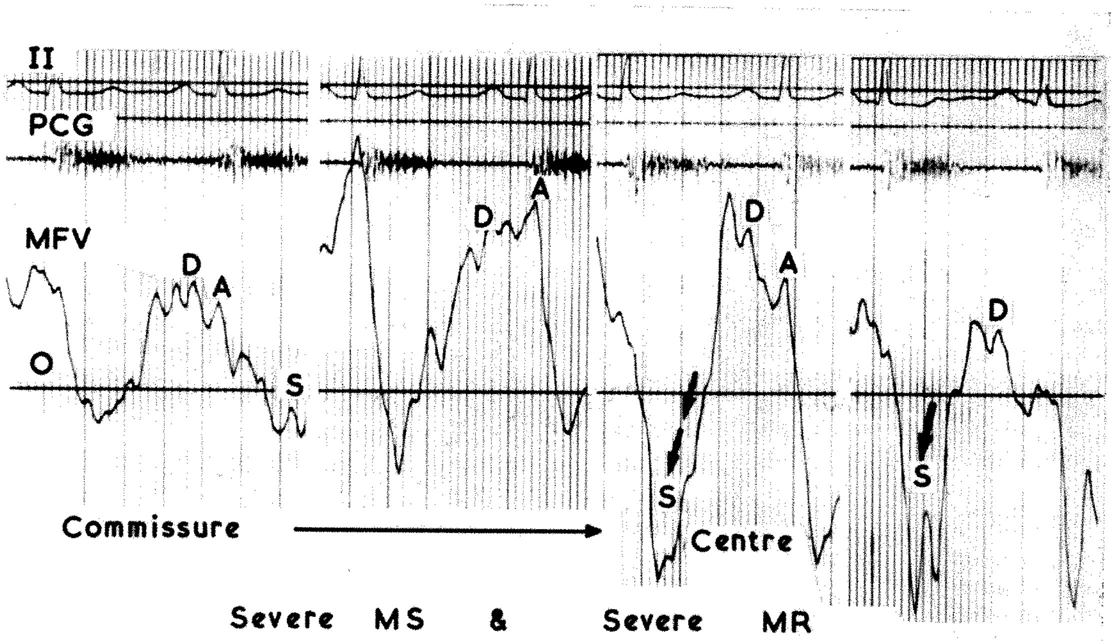

Fig. 13 *Mitral flow velocity patterns in severe stenosis associated with an important regurgitation. No backflow at the commissure and at the intermediary region, but the D wave is noticeably cut off and jagged, whereas at and near the centre a conspicuous negative systolic wave of large amplitude is elicited. Case 30, calculated mitral area 1·1 cm², regurgitation: 20 per cent of cardiac output.*

methods either in normal hearts or in animals or patients with mitral valve disease.

(a) The normal pattern recorded by transcutaneous pulsed Doppler ultrasound is strikingly similar to those provided by the electromagnetic cuff flowmeter surgically implanted in dogs or calves (Nolan *et al.*, 1969; Yellin *et al.*, 1970; Folts *et al.*, 1971) and also to those obtained in patients with normal mitral valve using the continuous wave Doppler transseptal catheterisation (Kalmanson *et al.*, 1975a).

(b) The recorded patterns in patients with mitral valve disease are also consistent with those obtained experimentally by Yellin in mitral stenosis and regurgitation (Yellin *et al.*, 1976), and peroperatively by Folts in patients with mitral regurgitation (Folts, 1976). The local velocities shown by the transcutaneous Doppler technique are also similar to the velocity profiles of Whamond (1976) obtained by using the pressure gradient technique in experimental mitral stenosis except perhaps for the amplitude of the wave.

(c) Further convincing evidence was provided in 10 of our patients in whom mitral valve flow velocity patterns could be recorded respectively (though not simultaneously) by intracardiac Doppler catheterisation and by the external technique. Both patterns turned out to be strikingly similar (Fig. 9–12).

It can therefore be concluded that the externally recorded curves actually represent the flow velocity pattern and are endowed with physiological or pathophysiological significance. The conclusions drawn from the studies of the curves recorded at the site of the mitral valve by intracardiac procedures (Kalmanson *et al.*, 1975a, b), also apply to those recorded externally, with the proviso that the peak velocity is not adequately represented whenever turbulent flow is present. In particular, the discussion and comments on the physiological interpretation of the normal curve, its relation to mitral flow involving the variations in size of the mitral annulus, the consequence of a flat profile in normal valves, as well as those in the interpretation of the anomalies shown on the tracings of patients with stenosis or regurgitation hold true for the external flow velocity curves.

It can, therefore, be stated that the indentations occurring on the D wave are most probably the result of *the turbulence generated by the stenosis*, whereas the negative systolic wave in mitral regurgitation represents *the backflow wave through the mitral annulus.*

EFFECT OF VELOCITY PROFILES

(1) The fact that the flow velocity profile in the normal valve is flat indicates that any recording made at any point of the annulus, except for a marginal region less than 5 mm from the ridge (Taylor and Wade, 1969) is representative of the mitral flow.

(2) This is not true in diseased valves, whose velocity profiles are irregular and asymmetrical (Kalmanson *et al.*, 1975b; Whamond and Taylor, 1976). This stresses the necessity for carefully exploring the various sites of the mitral annulus, lest one type of lesion is overlooked.

DIAGNOSTIC VALUE AND ASSESSMENT OF SEVERITY

Mitral stenosis

In our 16 patients with mitral stenosis, we consistently found anomalies of the D wave which consisted of indentations of the ascending limb or of its summit with a decreased slope, at one or several sites of the mitral annulus. These indentations may completely disappear at the centre (mild stenosis), occur late, and be of moderate importance in moderate lesions, and are early and coarse in all points of the mitral annulus in severe stenosis.

Mitral regurgitation

In our 9 patients with regurgitation, we consistently found a partly or entirely negative systolic wave at one or several sites of the mitral annulus. The amplitude, breadth, and width of the negative wave seem to correlate satisfactorily with the severity of the lesion. However, as previously mentioned, it must be emphasised that finding the negative wave may at times be difficult and time consuming, particularly in cases where the regurgitation is reduced to a localised jet, and *careful exploration of the entire annulus* at various angles may be necessary to establish the diagnosis.

On the other hand, false positive backflow wave may be present if the recorded blood sample is picked up too far away from the annulus and near the junction between the inflow and outflow tracts, where a physiological negative wave appears (Kalmanson *et al.*, 1972). Therefore, a careful check of the orientation of the transducer as well as of the accurate localisation of the gate at the mitral annulus is a prerequisite for any correct interpretation of a negative systolic wave. It is clear that this qualitative method cannot quantify the regurgitant fraction. However, whenever a careful exploration of the entire annulus is feasible, it seems possible to classify the regurgitation on a three-grade scale.

Combined lesions

In our 6 patients with associated stenosis and regurgitation, we consistently found the combined anomalies described above for each lesion, though these may not show up on the same record, making a thorough investigation of the mitral valve necessary.

Discrepancies In 3 other patients (cases 1, 8, and 14), in whom the conventional procedures did not disclose any regurgitation, the pulsed Doppler showed a minute (2 cases) to moderate (1 case) negative systolic wave, suggesting that the velocity recording might be more sensitive than the pressure or dye dilution techniques for detecting slight regurgitation.

It therefore can be stated that the transcutaneous pulsed Doppler technique appears to be a reliable aid to the diagnosis and assessment of severity of mitral valve disease, with the above mentioned limitations in respect of mitral regurgitation.

LIMITATIONS OF METHOD

(1) At present the method is not quantitative, but this does not affect the diagnostic value, since the latter relies exclusively on a pattern recognition method.

(2) The method is not always applicable, particularly in obese patients, or in subjects with dilated thorax or thoracic deformities.

Conclusion

In spite of some difficulties, the pulsed Doppler technique with analogue readout and associated with echocardiography provides a unique technique for studying mitral blood flow transcutaneously in a simple, safe, and repetitive way. In particular, in spite of some restrictions regarding mitral regurgitation, it turns out to be a reliable method for diagnosing, and assessing the severity of, mitral valve disease, by offering a direct graphic representation of phasic flow velocity disturbances which can be classified using a pattern recognition method. Moreover, it provides a new approach for studying mitral haemodynamic physiology and pathophysiology on a beat-to-beat basis.

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Potential pitfalls in quantification of pericardial effusions by echocardiography[1]

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In the echocardiographic assessment of patients with pericardial effusions, the apparent width of the echo-free space between the left ventricular posterior wall and the parietal pericardium is commonly used to estimate the amount of pericardial fluid present. In 4 patients with pericardial effusions, we showed a distinct disparity between the widths of the posterior pericardial space at different levels of the left ventricular posterior wall. In 2 of them, a 'swinging heart' appearance was recorded when the ultrasound beam was directed caudally, but not when its direction was cephalad or less caudad. It is suggested that the left ventricle should be scanned at all possible sites to minimise potential errors in estimating the amount of a pericardial effusion.

Since the pioneering studies of Feigenbaum *et al.* (1965), echocardiography has played an increasingly important role in the diagnosis and follow-up of patients with pericardial effusions. The next important advance occurred when Horowitz *et al.* (1974) correlated the amount of fluid within the pericardial cavity with the width of the echo-free space between the epicardium of the left ventricular posterior wall and the parietal pericardium. According to this method, which is now widely accepted and applied in routine clinical practice, the width of the sonolucent space between the left ventricular posterior wall and parietal pericardium, in systole and in diastole, is used to estimate the size of pericardial effusions. Moreover, the difference between the cubed diameters of the pericardium and epicardium at end-diastole is presumed to indicate the volume of pericardial fluid present (Horowitz *et al.*, 1974).

We have found, however, that the echocardiographic appearances in patients with pericardial effusions sometimes can be deceptive, and that on occasion the method of Horowitz *et al.* may yield ambiguous or inexact data unless certain precautions are taken in scanning technique. We do not claim to invalidate the technique of Horowitz *et al.* (which we have found reliable and useful in most patients with pericardial effusion), nor to introduce a new or different procedure for estimating the volume of pericardial fluid by echocardiography. We do wish to emphasise that in some patients with pericardial effusions, the nonuniform distribution of fluid within the pericardial sac may result in inaccurate data unless the echocardiographer is careful to visualise the ventricles at all levels, with all possible transducer directions.

In this report, we describe the echocardiograms of 4 representative patients with pericardial effusions in which we produced distinct variations in the width of the echo-free posterior pericardial space by scanning in different directions with the transducer. Thus, a cursory study might well have yielded an inaccurate estimation of the amount of pericardial fluid present.

Case reports

CASE 1

The echocardiogram (Fig. 1) of a 22-year-old man with chronic renal failure, hypertension, and sickle-cell disease was recorded with the transducer beam directed first to the aortic root and left atrium, then to the basal left ventricle at the level of both mitral cusps, and finally to the mid left ventricle at the level of the posterior mitral cusp only. The apparent diminution of the pericardial space posterior to the basal left ventricle is attributable to a solid layer (site marked X), which perhaps represents fibrinous material or granulation tissue, that is adjacent to, and seems to move with the parietal pericardium. However, as the transducer beam shifts laterally away from the anterior mitral cusp, the echo-free

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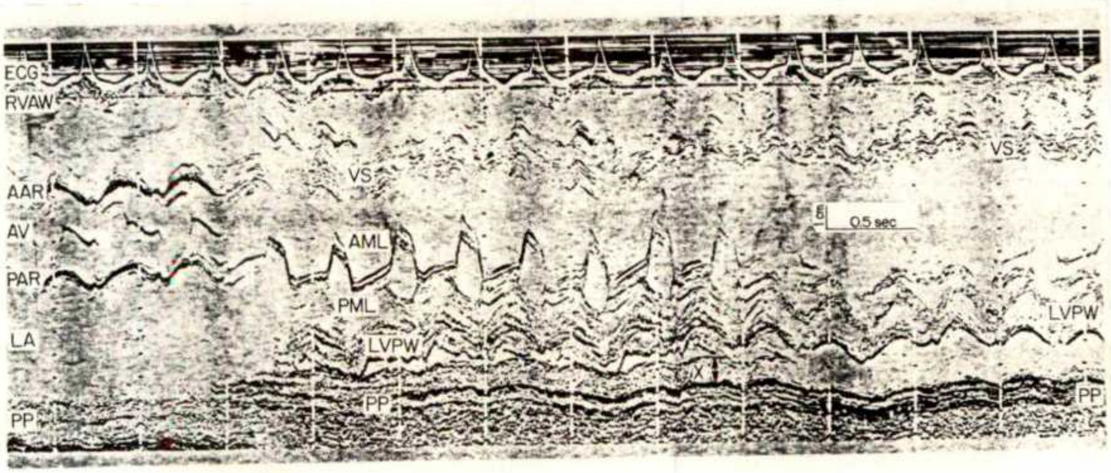


Fig. 1 *Echocardiogram of a 22-year-old man with pericardial effusion secondary to chronic renal failure. A scan was performed from aortic root (left), to basal left ventricle at the level of both mitral cusps (centre), and then to the mid left ventricle at the level of the posterior mitral cusp only (right). A sonolucent space, caused by posterior pericardial fluid is seen between the left ventricular posterior wall (LVPW) and parietal pericardium (PP). This pericardial space is much wider behind the mid left ventricle (right) than it is behind the basal left ventricle (centre) because of the solid layer of material (site marked X) contiguous to the pericardium behind the basal left ventricle. ECG, electrocardiogram; RVAW, right ventricular anterior wall; AAR, anterior aortic root; AV, aortic valve; PAR, posterior aortic root; LA, left atrium; VS, ventricular septum; AML, anterior mitral leaflet; PML, posterior mitral leaflet.*

pericardial space widens to about 2 cm, with disappearance of the solid layer.

CASE 2

During the examination of a 28-year-old woman in chronic renal failure, a scan was performed going from the mid left ventricle (at chordae level), to the basal left ventricle (at mitral valve level), and then to the aortic root and left atrium (Fig. 2A). Only a narrow echo-free space, wider in systole than in diastole, is visualised between the ventricular posterior wall and parietal pericardium at mid left ventricular level. This echo-free space widens considerably (to about 1·5 cm) behind the basal left ventricle, and then disappears abruptly as the transducer beam shifts from mitral valve to aortic root. A similar increase in the width of the pericardial space is seen (Fig. 2B) when another scan of the left ventricle was done from the level of the chordae tendineae to the level of the mitral valve. During the same study (Fig. 2C), a scan in the reverse direction was obtained by shifting abruptly the direction of the transducer from the region of the aortic root—left atrium to the mid left ventricle (level of the posterior mitral cusp and chordae tendineae), thereby missing or skipping the intermediate region of the basal left ventricle where both mitral cusps are visualised. Only a narrow echo-free space is detected posterior to the left ventricular posterior wall. On this scan (Fig. 2C) alone, the pericardial effusion appears to be small. However, if the mid left ventricle had not been scanned, the pericardial effusion would have been classified as moderate in size, since a wide separation is seen between the left ventricular posterior wall and the parietal pericardium at the basal left ventricular level (central segment of Fig. 2A, right segment of Fig. 2B).

CASE 3

This 35-year-old man developed a large pericardial effusion after irradiation of the mediastinum for Hodgkin's disease. The recording shown in Fig. 3A was obtained with the transducer placed on the chest wall adjacent to the sternal margin in the fourth left intercostal space and directed caudally and slightly medially; the recording shown in Fig. 3B was obtained with the transducer directed cephalad and slightly laterally. In panel A a 'swinging heart' appearance was obtained with an apparently small anteroposterior cardiac diameter and excessive cardiac mobility. Individual cardiac structures cannot be differentiated at first (left of panel A) but a slight shift in the direction of the transducer (right of panel A) makes it possible to distinguish the left ventricular posterior wall,

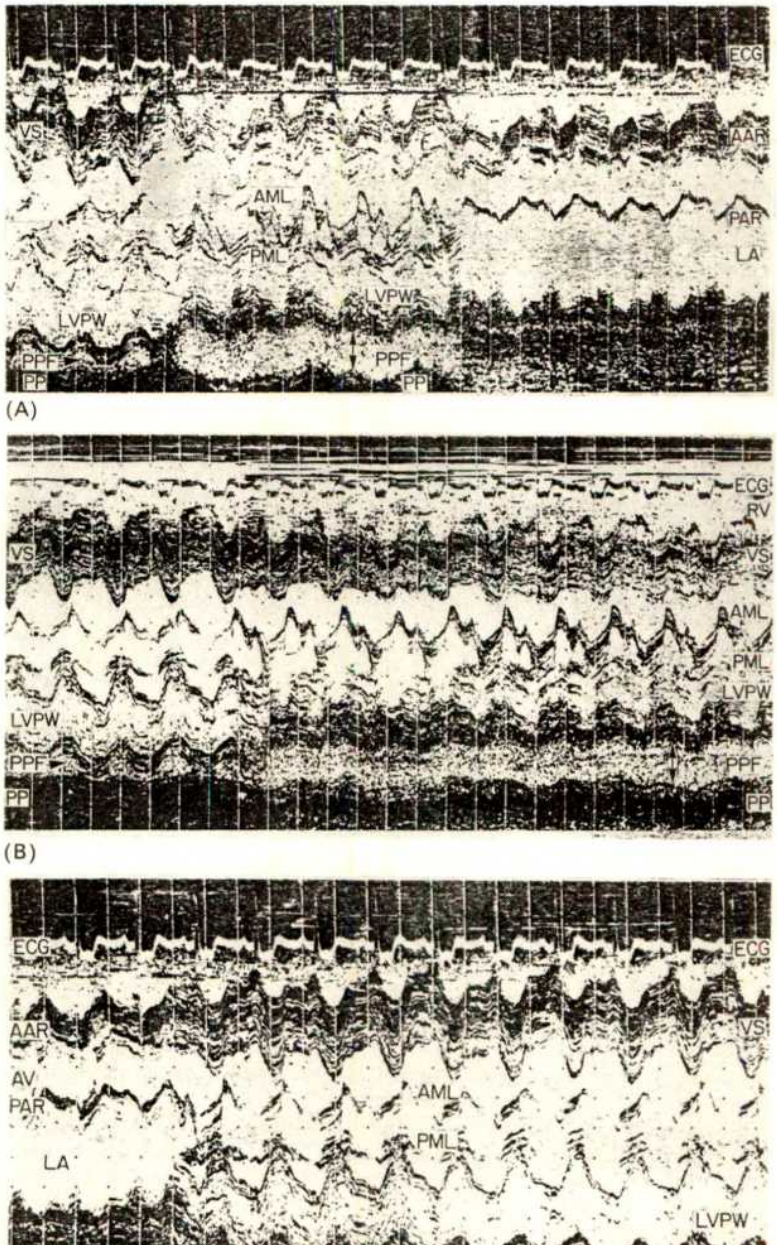


Fig. 2 *Echocardiogram of a 28-year-old woman in chronic renal failure. (A) A scan was performed from the mid left ventricle at chordae level (left), to the basal left ventricle at the level of both mitral cusps (centre), and then to the aortic root (right). The sonolucent space caused by posterior pericardial fluid is narrow behind the mid left ventricle but widens behind the basal left ventricle and ends abruptly as the aortic root and left atrium are visualised. (B) Another scan from mid (left) to basal left ventricle (right) again shows widening of the fluid-filled posterior pericardial space posterior to the basal left ventricle. (C) This scan was done from the aortic root (left) abruptly to the mid left ventricle (right), skipping the basal left ventricular region. The sonolucent space between the left ventricular posterior wall and parietal pericardium is narrow, suggesting a small pericardial effusion. (PPF, posterior pericardial fluid; other abbreviations as for Fig.) 1*

ventricular septum, and right ventricular anterior wall. In panel B the width of the anterior pericardial space remains approximately the same as in panel A, but the echo-free space between the left ventricular posterior wall and the parietal pericardium is less than in panel A, and the anterior mitral leaflet can be recognised in addition to the right ventricular anterior wall, ventricular septum, and left ventricular posterior wall. The appearance is no longer that of a 'swinging heart'. Immediately after

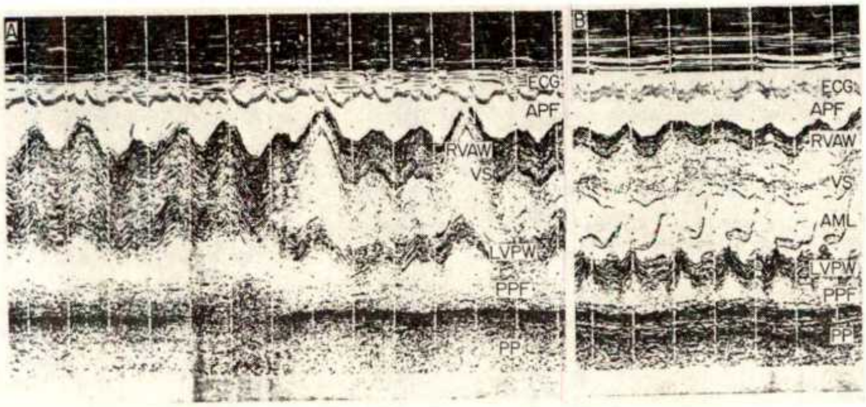


Fig. 3 *Echocardiogram of a 35-year-old man with a large pericardial effusion after mediastinal irradiation. (A) With the transducer directed caudally and slightly medially, a typical 'swinging heart' appearance is obtained (left) with a large pendulous or oscillatory motion of the heart within the pericardial fluid. Note that individual cardiac structures cannot be distinguished and that the total cardiac 'anteroposterior diameter' is relatively small. A slight shift in transducer direction (right of panel A) results in an increase in total cardiac diameter; the right ventricular anterior wall (RVAW), ventricular septum (VS), and the left ventricular posterior wall (LVPW) can just be recognised. APF, anterior pericardial fluid; PPF, posterior pericardial fluid. (B) The transducer was directed cephalad and slightly laterally. Whereas the anterior pericardial space remains about the same width as in panel A, the posterior pericardial space is much narrower than in panel A. The left ventricular posterior wall, anterior mitral leaflet (AML), ventricular septum, and right ventricular anterior wall can be identified easily.*

echocardiography, pericardial paracentesis yielded 1·5 litres of fluid.

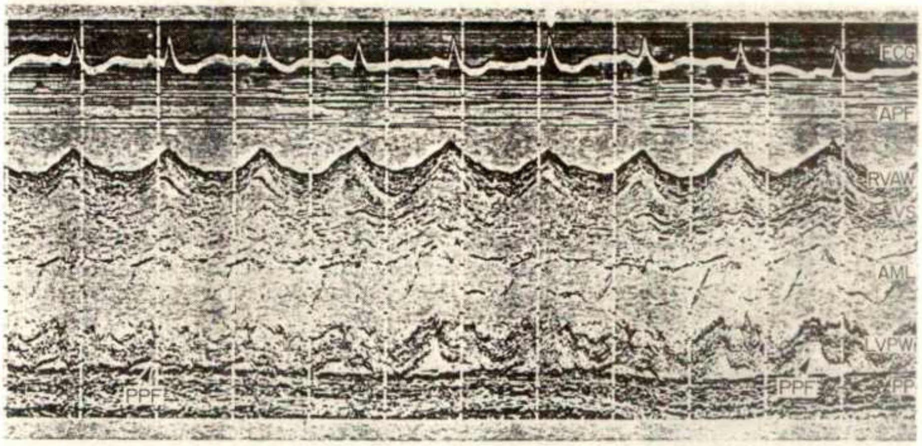
CASE 4

This 68-year-old man presented with a pericardial effusion one year after mediastinal irradiation for bronchogenic carcinoma. In the first four beats shown in Fig. 4A, the left ventricular posterior wall and parietal pericardium appear to be in contact during diastole, and separated by only 3 to 4 mm during systole. At this time the transducer was positioned in the fourth left intercostal space perpendicular to the chest wall. A slight lateral shift in the direction of the transducer reveals a larger amplitude of left ventricular posterior wall motion and a greater width (about 1 cm) of the echo-free space in systole, though the left ventricle still touches the parietal pericardium in diastole (last two beats of Fig. 4A). During the same examination, shift in the direction of the transducer medially and caudally (toward the right epigastrium) resulted in a 'swinging heart' appearance (left half of Fig. 4B). Pericardial paracentesis in this patient yielded 1 litre of fluid.

Discussion

Despite the widespread use of echocardiography for the diagnosis of pericardial effusion, uncertainty still exists in many patients about the precise amount and distribution of the effusion. Horowitz *et al.* (1974) have devised a semiquantitative method to assess pericardial effusions which assumes that the space occupied by the effusion between the left ventricular posterior wall and the parietal pericardium is of uniform width at all levels of the left ventricular posterior wall that are scanned (Fig. 5A). This assumption is essentially true in the majority of cases, and the method of Horowitz *et al.* has proved useful in routine clinical echocardiography. However, if the echo-free space should be wider at the level of the chordae tendineae (mid left ventricle) than at the level of the mitral valve (basal left ventricle) as in Fig. 1, one might conclude erroneously that the effusion is smaller than it actually is, unless the left ventricular scan includes the mid left ventricle (Fig. 5B). On the other hand, if a greater accumulation of pericardial fluid exists behind the basal left ventricle than behind the mid left ventricle as in Fig. 2, one might underestimate the size of the effusion if the change in transducer direction from the aortic root to mid left ventricle, or vice versa, is made too rapidly and thereby overlooks or skips the region of the basal left ventricle (Fig. 2C).

Horowitz *et al.* pointed out that 'factors determining the uniformity of distribution of pericardial fluid around the heart would influence the validity of



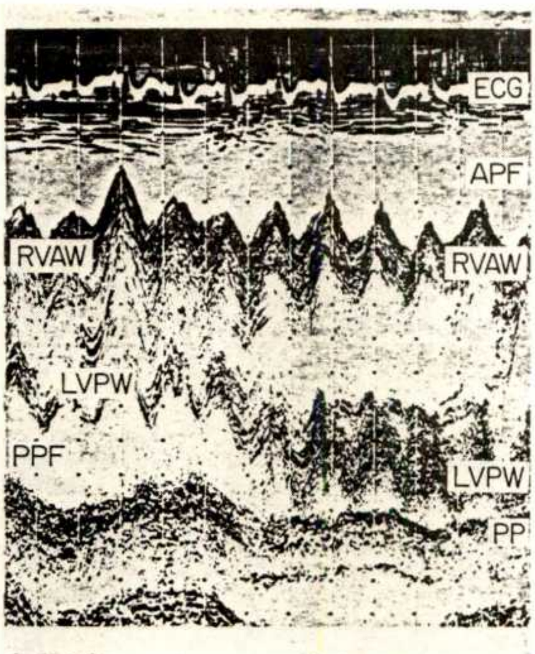


Fig. 4 *Echocardiogram of a 68-year-old man with a large pericardial effusion following mediastinal irradiation. (A) During the first 4 beats the transducer beam, directed perpendicular to the chest wall, transects the mid left ventricle, and a narrow separation is visualised in systole only between the left ventricular posterior wall and parietal pericardium. As the transducer beam was gradually shifted to the basal left ventricle (last 2 beats) the systolic separation increases. (B) When the transducer beam was directed caudally and medially, a typical 'swinging heart' appearance is obtained (left), with a relatively narrow 'anteroposterior' cardiac diameter which increases as the transducer beam is shifted to a slightly less caudal direction (right).*

calculation' of the volume of a pericardial effusion by their method. In some cases, loculation of pericardial fluid could conceivably be responsible for uneven distribution of pericardial fluid behind the left ventricular posterior wall (Fig. 5C). In addition, an apparent diminution in the echo-free space between the left ventricular posterior wall and the parietal pericardium can be caused by the presence of local adhesions or a solid structure within the pericardial sac that is localised to some area behind the left ventricular posterior wall. In our patient (Fig. 1), the solid material adherent to the parietal pericardium was probably an inflammatory or fibrinous plaque. Additionally, blood clots, malignant metastases, or tuberculous caseous material might intervene between the left ventricular posterior wall and the parietal pericardium in patients with pericardial effusions. An occasional

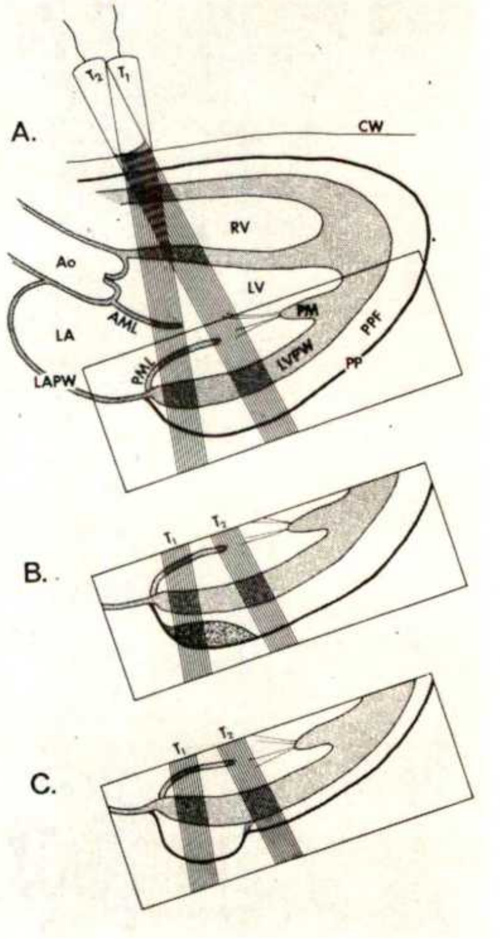


Fig. 5 *Diagrammatic section through the heart and pericardial sac in patients with pericardial effusions. In transducer position T1, the beam transects both mitral cusps (basal left ventricle). In transducer position T2, the beam transects only the posterior mitral cusp or chordae tendineae (mid left ventricle). (A) A uniform distance separates LVPW and parietal pericardium at all left ventricular levels. (B) Posterior pericardial fluid occupies a wider space behind the mid left ventricle (T2) than behind the basal left ventricle (T1). (C) Loculation of pericardial fluid causes it to accumulate to a greater extent behind the basal left ventricle (T1) than behind the mid left ventricle (T2). RV, right ventricle; LV, left ventricle; Ao, aortic root; LA, left atrium; LAPW, left atrial posterior wall; AML, anterior mitral leaflet; PML, posterior mitral leaflet; PM, papillary muscle; LVPW, left ventricular posterior wall; PPF, posterior pericardial fluid; PP, parietal pericardium.*

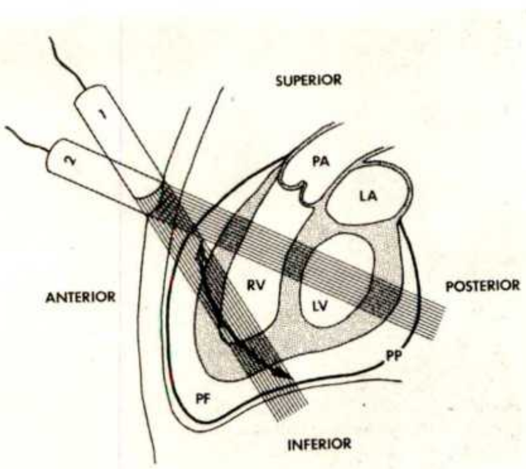


Fig. 6 *In the presence of a large pericardial effusion, a 'swinging heart' appearance may be recorded from the transducer position 1 because of the large amplitude of cardiac oscillation in this projection (indicated by arrows). The transducer beam transects mainly the lower right ventricle so that the 'anteroposterior cardiac diameter' appears relatively small. In transducer position 2, the beam transects the upper right ventricle, ventricular septum, and left ventricular posterior wall. At this level, the amplitude of cardiac oscillation is relatively small and the 'swinging heart' appearance is reduced. The anteroposterior diameter of the heart appears larger and individual cardiac structures such as the left ventricular posterior wall, ventricular septum, and mitral valve can be discerned. PA, pulmonary artery; PF, pericardial fluid.*

patient with a large pericardial effusion may have considerably more fluid around the cardiac apex than in the vicinity of the basal left ventricle (Chang, 1976).

The 'swinging heart' appearance, attributable to excessive oscillatory or pendulous motion of the heart within the pericardial fluid, is generally considered diagnostic of large pericardial effusions (Feigenbaum *et al.*, 1966; Gabor *et al.*, 1971; Feigenbaum, 1972). It is possible, however, to visualise gross to-and-fro motion of the heart as a whole when the transducer is directed caudally and medially, whereas with a cephalad or less caudad transducer direction, the echocardiographic appearance would indicate a pericardial effusion of only moderate (Fig. 3) or small (Fig. 4) size. The diagram in Fig. 6 depicts an explanation for these echocardiographic findings.

Thus, we suggest that every patient with a pericardial effusion should be scanned at all levels of the left ventricular posterior wall, which would entail a continuous scan from the aortic root to the left ventricle at the level of the mitral valve, that would then be continued laterally to include the distal left ventricle at the level of the chordae tendineae. We suggest further that when a 'swinging heart' appearance typical of pericardial effusion is detected, the beam should be shifted cephalad toward the base of the heart where the abnormal cardiac oscillations are of smaller magnitude (Fig. 6) to obtain a better delineation of individual cardiac structures.

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Comparison of dobutamine and dopamine in treatment of severe heart failure[1]

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The haemodynamic effects of dobutamine, a new synthetic catecholamine, were studied in 12 patients with severe congestive heart failure and compared with those of dopamine in 10 clinically similar patients. Dobutamine produced a distinct increase in cardiac index, while lowering left ventricular end-diastolic pressure and leaving mean aortic pressure unchanged. Dopamine also significantly improved cardiac index, but at the expense of a greater increase in heart rate than occurred with dobutamine. Dopamine was ineffective in lowering left ventricular end-diastolic pressure, but increased mean aortic pressure. We conclude that dobutamine is an effective, positive inotropic agent in patients with severe congestive heart failure. Because it has comparatively little effect on heart rate and aortic pressure, both major determinants of myocardial oxygen consumption, it may be of special value in patients with the low output syndrome associated with coronary heart disease.

The treatment of severe congestive heart failure continues to be a challenging problem in spite of many new and innovative pharmacological, mechanical, and surgical approaches. The sympathomimetic amines remain one of the primary forms of therapy because of their potent inotropic effect, yet none of those currently available for clinical use is wholly satisfactory. Noradrenaline produces excessive systemic vasoconstriction, decreasing tissue perfusion while increasing arterial pressure and cardiac work (Cohn and Luria, 1965; Vatner *et al.*, 1974a). Isoprenaline may increase heart rate and predispose to potentially fatal arrhythmias (Innes and Nickerson, 1975; Smith *et al.*, 1967). Peripherally, it induces beta-adrenergic vasodilatation, diverting cardiac output to noncritical tissues while lowering arterial and coronary perfusion pressure (Elliott and Gorlin, 1966; Gunnar *et al.*, 1967). In patients with coronary artery disease it may worsen myocardial ischaemia and increase infarct size (Maroko *et al.*, 1971; Lipp *et al.*, 1972). Dopamine is associated with considerably less chronotropic effect, but still may produce ventricular arrhythmias (Lipp *et al.*, 1972; Gunnar and Loeb, 1972). Though it lowers renal vascular resistance through stimulation of specific dopamine receptors, it has a predominantly alpha-adrenergic action on other arterial beds and may produce excessive vasoconstriction in high doses (McNay *et al.*, 1965; Goldberg, 1972; Vatner *et al.*, 1973). More importantly, dopamine's inotropic effect is mediated in part through the release of endogenous noradrenaline (Tsai *et al.*, 1967; Nash *et al.*, 1968). In severe heart failure, when endogenous noradrenaline stores are low, its ability to improve cardiac output may be reduced and unpredictable (Chidsey *et al.*, 1963; Tuttle and Mills, 1975).

Dobutamine ([±]-4-[2-[[3-(p-hydroxyphenyl)-1-methyl propyl] amino] ethyl] pyrocatechol hydrochloride) is a new synthetic sympathomimetic amine developed in an effort to reduce the deleterious effects associated with currently available inotropic agents (Tuttle and Mills, 1975). Though a derivative of dopamine, it acts directly on adrenergic receptors rather than through release of endogenous noradrenaline. Preliminary studies indicate that it dramatically improves cardiac output with relatively little chronotropic or peripheral vascular effect (Gunnar *et al.*, 1973; Vatner *et al.*, 1974b; Robie *et al.*, 1974; Akhtar *et al.*, 1975). It remains to be established, however, whether dobutamine is clinically a more effective therapeutic agent. Accordingly, this study was undertaken to assess the degree of haemodynamic improvement produced by dobutamine in patients with severe heart failure and

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to compare its effects with those of dopamine in a similar group of patients.

Methods

Twelve patients undergoing routine diagnostic cardiac catheterisation were studied. All had evidence of severe left ventricular dysfunction, either on the basis of coronary artery disease or cardiomyopathy. None had significant valvular abnormalities.

At the end of the diagnostic cardiac catheterisation, control haemodynamic measurements were made, including right atrial, pulmonary artery, pulmonary capillary wedge, left ventricular, and aortic pressures. Cardiac output was measured using the Fick method. Arterial and mixed venous oxygen content were determined using an Instrumentation Laboratory spectrophotometer. From these, systemic and pulmonary vascular resistances were calculated. Maximal left ventricular dp/dt was obtained by computer analysis of the left ventricular pressure tracing. Left ventricular pressures were recorded through fluid-filled catheters which had been tuned and optimised to provide linear frequency responses up to 16 Hz. These frequency responses have been shown to provide data necessary to obtain high quality left ventricular dp/dt measurements. After recording control values, dobutamine was infused intravenously at a rate of 10 µg/kg per min for 15 minutes and the above measurements were repeated.

Haemodynamic data from 10 different patients with similar haemodynamic derangements previously studied in our laboratory during dopamine administration are presented for comparison (Holloway *et al.*, 1975). All had severe left ventricular dysfunction without evidence of significant valvular abnormalities. Control haemodynamic measurements were made as described above. An infusion of dopamine (100 µg/ml) was begun at a rate of 2 µg/kg per min for 5 minutes, then increased by 2 µg/kg per min every 5 minutes until mean aortic pressure increased by 15 mmHg or heart rate by 30 beats/min. When either of these limits was reached, the infusion rate was kept constant for an additional 5 minutes and the haemodynamic measurements were repeated. The rate required to obtain the desired end-point ranged from 2 to 16 µg/kg per min.

Table 1 *Haemodynamics in 12 patients with severe left ventricular failure before and after dobutamine infusion (mean ± SEM)*

	Control	*Dobutamine*
Heart rate (beats/min)	90·1 ±4·0	102·7 ±4·0*
Right atrial mean (mmHg)	5·0 ±1·9	2·0 ±1·0*
Pulmonary artery mean (mmHg)	36·8 ±2·9	34·9 ±4·1
Pulmonary capillary wedge mean (mmHg)	22·0 ±2·4	17·9 ±3·2*
Left ventricular end-diastolic (mmHg)	28·3 ±2·4	21·5 ±2·9*
Aorta mean (mmHg)	82·0 ±3·3	82·0 ±5·6
Cardiac index (l/min per m^2)	1·9 ±0·1	3·5 ±0·4*
Stoke index (ml/beat per m^2)	22·2 ±1·7	32·1 ±2·5*
Systemic vascular resistance (Wood units)	22·1 ±1·4	14·2 ±2·0*
Pulmonary vascular resistance (Wood units)	4·2 ±0·5	2·9 ±0·4*
Left ventricular dp/dt (mmHg/s)	842·5 ±99·9	1337·9 ±228·0*

*P < 0·05.

All statistical analyses were performed using Student's t-test for paired samples, or for unpaired samples with equal variance, and a P value of less than 0·05 was taken as indicative of statistical significance.

Results

The haemodynamic response to dobutamine infusion in 12 patients with severe left ventricular dysfunction is summarised in Table 1. The cardiac index increased dramatically from 1·9 to 3·5 l/min per m^2, largely because of an increase in stroke index (P < 0·001). This was accompanied by a fall in left ventricular end-diastolic pressure from 28·3 to 21·5 mm (P < 0·001) and a nearly 60 per cent rise in left ventricular dp/dt (P < 0·005). Mean aortic pressure remained constant, while calculated systemic vascular resistance fell by 36 per cent. Mean pulmonary artery pressure was unchanged, while pulmonary vascular resistance was reduced by 31 per cent. Heart rate was increased by a mean of 13 beats/min.

The haemodynamic response to dopamine infusion in 10 similar patients with left ventricular dysfunction is summarised in Table 2. These results form part of an earlier report (Holloway

Table 2 *Haemodynamics in 10 patients with severe left ventricular failure before and after dopamine infusion (mean ± SEM)*

	Control	*Dopamine*
Heart rate (beats/min)	82·1 ±4·1	110·9 ±5·9*
Right atrial mean (mmHg)	6·3 ±1·2	7·9 ±1·5
Pulmonary artery mean (mmHg)	38·2 ±2·3	48·5 ±4·2*
Pulmonary capillary wedge mean (mmHg)	24·4 ±1·3	28·4 ±2·6
Left ventricular end-diastolic ((mmHg)	28·8 ±1·4	30·4 ±2·9
Aorta mean (mmHg)	85·4 ±3·1	98·4 ±4·6*
Cardiac index (l/min per m^2)	2·0 ±0·2	3·0 ±0·3*
Stroke index (ml/beat per m^2)	24·4 ±1·9	27·0 ±2·4
Systemic vascular resistance (Wood units)	24·0 ±2·2	17·4 ±1·7*
Pulmonary vascular resistance (Wood units)	4·5 ±0·9	4·3 ±0·8

*P < 0·05.

et al., 1975). Control cardiac index, left ventricular end-diastolic pressure, mean aortic and pulmonary arterial pressures, systemic vascular resistance, pulmonary vascular resistance, and heart rate are similar to those of the 12 patients receiving dobutamine. Cardiac index increased significantly after dopamine administration, though to a lesser degree than with dobutamine. Left ventricular end-diastolic pressure was unchanged, while mean aortic and pulmonary arterial pressures increased. Heart rate rose by a mean of 29 beats/min, significantly greater than with dobutamine ($P < 0{\cdot}05$). while stroke index increased by only 11 per cent.

Discussion

Previous work has shown dobutamine to be a potent and relatively selective inotropic agent with only minor chronotropic and peripheral vascular effect (Vatner *et al.*, 1974b; Robie *et al.*, 1974; Akhtar *et al.*, 1975; Gunnar *et al.*, 1973; Tuttle and Mills, 1975). This study extends these findings to a group of patients with severe heart failure resulting from coronary artery disease or cardiomyopathy, in whom dobutamine might be clinically indicated. When infused at a rate of 10 μg/kg per min, dobutamine dramatically improved left ventricular function, increasing left ventricular dp/dt by over 50 per cent, nearly doubling cardiac index, and lowering left ventricular end-diastolic pressure. Dobutamine reduced peripheral vascular resistance and some of its effect could be attributed to this reduction in afterload. The increase in cardiac output and the drop in left ventricular end-diastolic pressure would be influenced by this peripheral vasodilatation. In contrast, the administration of dopamine failed to reduce left ventricular end-diastolic pressure. This lack of reduction of left ventricular end-diastolic pressure could be attributed to the observation that there was an increase in arterial pressure or afterload, since by other measures dopamine clearly produced an inotropic effect. Heart rate rose by 14 per cent, while a nearly 50 per cent increase in stroke index accounted for the majority of the improvement in cardiac output. Mean systemic arterial pressure remained unchanged because of a 36 per cent decline in systemic vascular resistance, the latter reflecting either a reflex reduction in sympathetic tone or a direct effect of dobutamine on the peripheral vasculature.

Comparison of these findings with the haemodynamic effects of dopamine in a similar group of patients, previously studied in our laboratory, reveals several important differences. Dopamine, while administered in doses that significantly increased cardiac index, was ineffective in lowering left ventricular end-diastolic pressure from levels commonly associated with pulmonary oedema. As a result its use may be associated with continued pulmonary vascular congestion and arterial desaturation (Loeb *et al.*, 1975).

Although both drugs produced similar increases in cardiac index with the doses employed, dopamine accomplished this at the expense of a significantly greater increase in heart rate. Systemic arterial pressure also rose with dopamine administration, in spite of a slight decrease in systemic vascular resistance. Since both heart rate and arterial pressure are important determinants of myocardial oxygen consumption (Sonnenblick and Skelton, 1971), these findings suggest that dobutamine may be preferable in treating patients with coronary artery disease. Animal studies using epicardial ST segment mapping and coronary sinus lactate determinations have shown that dopamine may worsen myocardial ischaemia and injury after coronary occlusion (Stemple *et al.*, 1976). In contrast, when dobutamine was administered to patients in clinical heart failure with evolving myocardial infarctions, there was no detectable increase in myocardial injury as determined by hourly serum-CK determinations and a plot of the CK-kinetic curves (Gillespie *et al.*, 1975).

Similarly, dobutamine's pharmacological actions offer distinct advantages over the other currently available inotropic agents. In equivalent doses it induces far less tachycardia than isoprenaline and is not associated with excessive vasodilatation or hypotension (Tuttle and Mills, 1975; Vatner *et al.*, 1974b; Robie *et al.*, 1974). At the other end of the spectrum, the pronounced vasoconstriction that occurs with noradrenaline is also avoided. Instead, dobutamine acts more selectively to improve myocardial contractility and left ventricular function, with tissue perfusion increasing in proportion to cardiac output.

While it is difficult to extrapolate directly to patients treated in the hospital with low cardiac output resulting from cardiomyopathy, we believe that our studies clearly show the effectiveness of dobutamine. Because of its predictable inotropic effects while producing little in the way of increased myocardial oxygen demands, we believe it deserves use in patients with the low output syndrome associated with coronary heart disease.

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Comparison of lidoflazine and quinidine in prophylactic treatment of arrhythmias

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The efficacy of quinidine versus lidoflazine therapy was compared in the maintenance of sinus rhythm after electrical cardioversion for atrial flutter or fibrillation in a group of 35 patients. Both quinidine and lidoflazine were relatively ineffective in maintaining sinus rhythm after cardioversion. Lidoflazine was also used to prevent supraventricular and ventricular tachycardias in a miscellaneous group of patients; one of these with paroxysmal supraventricular tachycardia developed runs of ventricular tachycardia soon after starting lidoflazine. The trial was stopped after 4 patients died while receiving lidoflazine, on the suspicion that their deaths may have been related to drug-induced arrhythmias. The arrhythmogenic potential of lidoflazine when used in patients with supraventricular arrhythmias contrasts with reports of its apparent safety in large numbers of patients with angina pectoris.

Despite the high initial success rate in the treatment of atrial flutter and atrial fibrillation by electrical cardioversion, it has been the experience of most workers that sinus rhythm can be expected to persist in only approximately 20 per cent of patients at the end of one year (Coelho *et al.*, 1967; Bjerkelund and Orning, 1968; Radford and Evans, 1968; Södermark *et al.*, 1975). Our similarly unsatisfactory results despite the use of maintenance quinidine gluconate and a recent report of sinus rhythm in 90 per cent of patients at one year after cardioversion while receiving maintenance lidoflazine (Batloun, 1970) led us to undertake a comparison of its efficacy with that of quinidine gluconate.

Lidoflazine is the generic name of 1–/4, 4–di–(fluoro-phenyl)-butyl/–4–(2,6-dimethyl-anilino-carbonyl)-methyl/–piperazine with the following structural formula (Fig. 1).

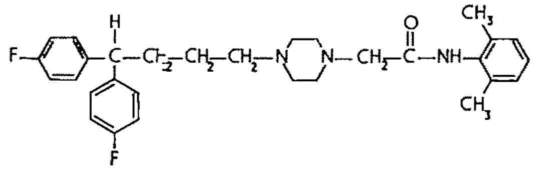

Fig. 1 *Chemical formula.*

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It has been shown in animal experiments to have a prolonged coronary vasodilator effect by direct action on the smooth muscle of the coronary arteries (Schaper *et al.*, 1965, 1966), and its antiarrhythmic properties in animals have been described by Carmeliet and Xhonneux (1971). It has been extensively used clinically in the treatment of angina pectoris and in the conversion of atrial fibrillation to sinus rhythm.

Subjects and methods

Patients entering the trial were under 70 years of age and had to remain in sinus rhythm for at least 24 hours after cardioversion. Patients with recent myocardial infarction, active myocarditis, cardiac surgery less than one month previously, known sensitivity to lidoflazine or quinidine, a blood urea above 60 mg/100 ml (9·9 mmol/l), a platelet count under 100 000/mm^3, or serum potassium levels under 4·0 mmol/l were excluded. Patients with ventricular premature systoles occurring more frequently than 5 times per minute or where the ventricular extrasystoles were multifocal, consecutive, or had a QR/QT ratio less than 1 were also excluded. Relapse after previous cardioversion did not exclude patients from entry to the trial.

Before cardioversion patients underwent routine physical examination, 12-lead electrocardiogram with 12-second rhythm strip, and chest *x*-ray examination. Blood was checked for electrolytes, urea, creatinine, and platelets. Digoxin was withheld for at least 12 hours before cardioversion. After cardioversion, a test dose of quinidine sulphate (200 mg) or lidoflazine (60 mg) was given in all cases.

Therapy was designed so that patients were randomly allocated after electrical cardioversion to either a low-dose lidoflazine (60 mg 8-hourly) or quinidine gluconate (324 mg 8-hourly) group. If relapse occurred on this therapy, the higher dose of the same drug (lidoflazine 120 mg 8 hourly or quinidine gluconate 648 mg 8-hourly) was then prescribed after reconversion. Further relapse resulted in the patient being switched to the opposite drug group at low dosage after cardioversion, and finally a further relapse necessitated repeat cardioversion and the higher dosage of the opposite drug.

Follow-up examinations were undertaken at 1, 3, 6, and 12 months after cardioversion, with the intention to continue them for 2 years if the trial had run its course. The electrocardiogram, blood electrolytes, urea, creatinine, and platelets were checked at each outpatient visit after cardioversion. Patients were removed from the trial where symptoms were thought to be attributable to side-effects of the drug. Patients who failed to take their drugs as prescribed were also removed from the trial, as were patients in whom the electrocardiogram showed widening of the QRS complex, atrioventricular dissociation, or the development of ventricular extrasystoles fulfilling the original criteria preventing inclusion in the trial.

Twenty-two patients received low dose quinidine gluconate and three subsequently received the higher dosage after a second cardioversion, having relapsed into atrial flutter/fibrillation. Fourteen patients received low dose lidoflazine and one of these went on to the higher dosage after relapse and repeat cardioversion. Two patients received low dose lidoflazine, after reversion to atrial flutter/fibrillation on both low and high dose quinidine gluconate.

The average age of the patients allocated initially to quinidine gluconate therapy (37·9 years) did not differ significantly from that of the group receiving lidoflazine therapy (44·4 years). Just over half the patients in each group had underlying rheumatic heart disease while the remainder had an approximately equal distribution of either cardiomyopathy, ischaemic, congenital, hypertensive, or no apparent underlying heart disease. The cardiothoracic ratio exceeded 50 per cent in exactly half the patients in each group. The duration of the atrial flutter/fibrillation was 3 months or longer in 11 of the patients treated initially with quinidine gluconate and 9 of those treated initially with lidoflazine. Atrial fibrillation had been present for 6 months or more in 6 patients in each group and for one year or longer in 4 patients in each group.

Results

The Table illustrates the proportion of patients holding sinus rhythm at varying periods after cardioversion and takes into account the diminishing population over the months resulting from patients defaulting or stopping therapy because of side-effects and eventually from the trial being stopped. It will be seen that approximately half of the patients on low dose lidoflazine or quinidine were still in sinus rhythm 6 months after cardioversion. Of the 3 patients who failed to maintain sinus rhythm on high dose quinidine, 1 failed to reconvert, 1 became depressed after 2 weeks on lidoflazine, and the third maintained sinus rhythm for the 16 weeks she received it. Of the 2 patients who failed to maintain sinus rhythm while on low dose lidoflazine, 1 patient was switched to high dose lidoflazine but died shortly after.

Five of the patients receiving quinidine gluconate and 1 of the patients receiving lidoflazine stopped treatment. Three other patients discontinued quinidine gluconate therapy because of gastro-intestinal side-effects, 1 developed cinchonism, one developed thrombocytopenic purpura, and quini-

Table

	No. of patients		*Time after conversion*					
			1 month	*2 month*	*3 month*	*4 month*	*5 month*	*6 month*
Low dose quinidine	22	In sinus rhythm	13	11	10	7	4	4
		Relapsed	2	2	2	2	2	2
High dose quinidine	3	In sinus rhythm	2	1	0			
		Relapsed	1	1	2			
Low dose lidoflazine	14	In sinus rhythm	8	7	5	3	2	2
		Relapsed	1	1	2	2	2	2
High dose lidoflazine	1	In sinus rhythm	0					
		Relapsed	0					

dine was withdrawn in one because of development of frequent ventricular extrasystoles. One patient developed a desquamative rash on the palms of the hands while receiving quinidine and later when he was switched to lidoflazine therapy as well. One patient on lidoflazine treatment became depressed.

Among those taking lidoflazine 4 died suddenly and unexpectedly between eight days and 25 weeks after starting therapy. Three of them were receiving low dose lidoflazine and the other one was on the higher dose regimen. These deaths led to the trial being abandoned at the advice of the Hospital Pharmaceutical Advisory Committee and the Faculty Review Committee for Clinical Research Investigation. Case summaries for the 4 patients concerned are reported in detail.

CASE 1

This 67-year-old woman had been followed for 9 years with hypertension, diabetes, and severe peripheral vascular disease for which bilateral above-the-knee amputations had been performed. Her hypertension was severe, requiring methyldopa and Rautrax, while her diabetes was mild and was controlled on oral therapy plus diet. She had well-controlled cardiac failure for which she received digoxin and frusemide with potassium supplements. Since 1964 she had been known to have an electrocardiogram showing left bundle-branch block with left axis deviation, and in December 1968 she presented with a history of syncope and was shown on Holter monitoring to have periods of sinus bradycardia as low as 37/minute, periods of atrial fibrillation, and periods of sinus rhythm with first degree block in addition to her left bundle-branch block and left axis deviation. A permanent transvenous pacemaker was implanted resulting in control of her syncopal attacks. Thereafter she was found to be in sinus rhythm on all subsequent follow-up visits to the Pacemaker Clinic. In December 1971 she had a transient cerebrovascular accident from which she made a good recovery. In August 1973 she presented in rapid atrial fibrillation and was given digitalis. Despite this, dyspnoea failed to improve and atrial fibrillation persisted. She was, therefore, cardioverted on 22 October 1973 at which time she had serum potassium values between 4·4 and 5·1 mmol/l. After cardioversion her electrocardiogram showed sinus rhythm at 70/minute, PR interval 0·20 s, left axis deviation, and complete left bundle-branch block. She was discharged on frusemide 80 mg daily, potassium chloride 1200 mg t.d.s., phenformin HCl 50 mg daily, and lidoflazine 60 mg 8 hourly. It was learnt subsequently that she died 8 days after cardioversion. Since her cardioversion she had been resting at home and complained of occasional chest pain. She spent the day alone and was found lying dead on the floor that evening, having fallen from her wheelchair. Necropsy was not obtained.

CASE 2

This 42-year-old woman was first seen in April 1969 after a transient cerebrovascular accident resulting from presumed cerebral embolism complicating atrial flutter/fibrillation with underlying mitral stenosis and trivial aortic regurgitation. She was cardioverted for the first time in July 1969 and again in February 1973 for recurrence of atrial fibrillation and on each of these occasions she was maintained on quinidine sulphate 400 mg 8 hourly after conversion. In October 1973 she was cardioverted for a third time after which she received lidoflazine 60 mg 8 hourly, diazepam 2 mg t.d.s. while warfarin was continued. At that stage she was asymptomatic, with signs of non-critical mitral stenosis and trivial aortic regurgitation and her electrocardiogram showed sinus rhythm with a PR interval of 0·20 s, left axis deviation, and complete left bundle-branch block. When seen at follow-up 1 month and 3 months after cardioversion she was well and was taking her therapy. Her electrocardiogram showed sinus tachycardia on each occasion with a normal PR interval and persistent left axis deviation and complete left bundle-branch block. The QT interval varied from 0·36 to 0·37 s. Serum potassium level at her last follow-up visit was 4·6 mmol/l. Two days before her death she was seen by her general practitioner who said that she appeared well with a normal pulse rate. Twenty-five weeks after cardioversion she was seen by her family at 7 a.m. and appeared to be well but was found dead in bed 20 minutes later. There were no preceding warning symptoms of syncope or palpitations to suggest an arrhythmic mode of death. Necropsy was not obtained.

CASE 3

This man was 33 years old when he developed palpitations. His referring physician found him to have tachycardia and started him on propranolol 40 mg daily and frusemide 40 mg on alternate days. There was a history of an acute myocardial infarction at the age of 30 years confirmed by review of the electrocardiograms at that time. After his infarct he had led an active life without restriction during the 3 years before his death and he was not unduly disturbed by the development of the arrhythmia.

On physical examination he appeared to be nervous and his electrocardiogram showed evidence of atrial flutter with 4:1 atrioventricular block. He was cardioverted and started on lidoflazine 60 mg

8 hourly on 7 December 1973. After cardioversion, clinical examination indicated cardiomegaly with a loud third heart sound and a grade 2/6 systolic ejection murmur at the base. Chest *x*-ray examination confirmed the presence of significant cardiomegaly. A clinical diagnosis of thyrotoxicosis was suggested and serum T3 and T4 were sent for analysis. The possibility of alcoholic cardiomyopathy was also entertained as there was a history of excessive alcoholic intake over many years. At the time of discharge on lidoflazine therapy alone his serum potassium was 4·0 mmol/l and his discharge electrocardiogram showed a sinus tachycardia of 108/minute with a normal PR interval, normal frontal axis, left atrial and left ventricular enlargement which had not been present at the time of his previous myocardial infarction; the QT interval was 0·36 s.

It was learnt that the patient died suddenly 31 days later. His wife said that he started making noises during the night and she awoke to find him unconscious and cyanosed; by the time the doctor arrived he was dead. He had been seen by several people during the days before his death and he was described as being asymptomatic and in apparent good health. In particular there was no story of syncope or dizzy spells before his death. After his death results of thyroid function tests became available which were clearly abnormal with a T3 value of 58 μg/100 ml and T4 of greater than 25 μg/100 ml. In retrospect, he presumably had thyrotoxic as well as ischaemic heart disease. Necropsy was not obtained.

CASE 4

This 49-year-old woman had been followed for 11 years with mitral regurgitation which had first been detected at the age of 15 years. She had grade 2/4 effort intolerance for which she had been given digitalis and she had received frusemide 80 mg daily and potassium chloride 1200 mg t.d.s. She first went into atrial fibrillation in August 1974 and was started on lidoflazine 60 mg 8 hourly plus her other medications after cardioversion in November 1974. She underwent dilatation and curettage for irregular menstrual bleeding three weeks later having previously undergone a similar operation uneventfully in 1968. Because she had relapsed into atrial fibrillation since her previous cardioversion she was cardioverted later on the day of operation and restarted on lidoflazine at the higher dosage of 120 mg 8 hourly. After cardioversion she was in sinus rhythm with a normal PR interval and slight non-specific QRS widening of 0·10 s, with additional electrocardiographic evidence of left atrial and left ventricular enlargement. Chest *x*-ray examination showed left ventricular cardiomegaly. Her postoperative recovery was uneventful until the morning of the third postoperative day when she was due to be discharged from hospital. When her routine temperature was taken at 5 a.m. she was found to be well but 30 minutes later she collapsed and died. Permission for necropsy was refused. A serum potassium performed the previous month had been 4·2 mmol/l. Review of her drug chart indicated that she had been receiving her lidoflazine therapy in a dose of 60 mg 8 hourly as prescribed, and that after cardioversion the dosage was increased to 120 mg 8 hourly which she received until the night before her death at 10 p.m. This meant that her previous dose had been given seven and a half hours before her death and that the increased dosage of lidoflazine had been administered for two and a half days before she died.

Discussion

A valid comparison of the efficacy of quinidine versus lidoflazine in maintaining sinus rhythm after cardioversion for atrial flutter and atrial fibrillation in the two groups of patients could not be made in this abortive trial and a limited number of patients only received both quinidine and lidoflazine. Though less than half the patients who remained in the trial were still in sinus rhythm 6 months after cardioversion the numbers are far too small for comparison of the relative effectiveness of the two drugs. As seen in previous trials, however, the relapse rate was higher in the first three months than in the second three months after cardioversion (Coelho *et al.*, 1967; Bjerkelund and Orning, 1968; Cramér, 1968). Comparison between the patients entering the two groups in terms of the nature of underlying heart disease, cardiac size, and previous duration of atrial fibrillation, factors known to influence the duration of sinus rhythm after cardioversion, indicated a surprising similarity in this small group of patients.

Side-effects were seen in patients on both drugs and most of these were well-recognised complications such as gastrointestinal upsets, cinchonism, rash, and thrombocytopenic purpura with quinidine therapy. The occurrence of rash or depression with lidoflazine therapy, however, has not previously been described to my knowledge.

The most striking feature that emerged from this trial and the reason for abandoning it before completion was the unexpected occurrence of 4 deaths among the patients receiving lidoflazine, while none of the patients receiving quinidine succumbed. Most patients qualifying for entry to such a trial have serious underlying heart disease and are at risk of sudden death from a variety of mechanisms related to their disease processes (Cramér, 1968; Takkunen *et al.*, 1970).

The phenomenon of quinidine-induced ventricular tachycardia and ventricular fibrillation is a well-documented one (Oram and Davies, 1964; Selzer and Wray, 1964; Bjerkelund and Orning, 1968; Cramér, 1968; Radford and Evans, 1968) and constitutes a rare but well-recognised cause of sudden death (Maurice *et al.*, 1956; Radford and Evans, 1968). There have been similar previous reports of syncope, paroxysmal ventricular tachycardia or ventricular fibrillation, and sudden death in patients receiving lidoflazine therapy (Miyahara *et al.*, 1969; Batlouni, 1970; Piessens *et al.*, 1970; Bortoluzzi and Rodrigues, 1971; Schlepper and Derro, 1972; Czerny *et al.*, 1975). In all instances lidoflazine was being given, in order to convert atrial tachyarrhythmias to sinus rhythm, in similar doses to those used to maintain sinus rhythm in this study. Among the 206 patients in these six reports the incidence of these problems was 14 per cent. There are other reported series, however, comprising a total of 57 patients without any of the above dangerous complications (De Vil and Bruyneel, 1974; Bruyneel *et al.*, 1975; Lehmann and Hochrein, 1975). Among the numerous reported series of patients receiving quinidine for medical cardioversion the highest reported incidence of syncope is 6·8 per cent among 237 patients (Cramér, 1968). Though the comparative risks of lidoflazine versus quinidine therapy have not been systematically evaluated these reports plus the present one suggest that lidoflazine is the more hazardous of the two drugs.

During the course of this trial we tried the effect of lidoflazine in the same dosage in a miscellaneous group of 14 patients consisting of 3 with paroxysmal supraventricular tachycardia, 3 with paroxysmal ventricular tachycardia, and 8 who had been electively cardioverted from atrial flutter/fibrillation but who could not enter the trial because of previously known gastrointestinal intolerance to quinidine. Though there were no deaths in this group, one 75-year-old woman with paroxysmal supraventricular tachycardia and occasional ventricular extrasystoles developed runs of self-limiting ventricular tachycardia during lidoflazine therapy (Fig. 2). Lidoflazine was stopped and lignocaine administered with adequate control of her arrhythmia. Serum potassium was checked and found to be above 5 mmol/l on several occasions. Eighteen hours after stopping lidoflazine a test dose of 200 mg quinidine sulphate and 8 hours later quinidine gluconate 648 mg 8 hourly was begun. Lignocaine had now been withdrawn and on quinidine therapy extrasystoles again increased as did frequent runs of ventricular tachycardia. She developed paroxysms of ventricular fibrillation, one of which was persistent with loss of consciousness requiring defibrillation. Quinidine was immediately withdrawn and intravenous lignocaine restarted, with signs of ventricular irritability subsiding within the next few days. Paroxysmal supraventricular tachycardia was eventually controlled on practolol 100 mg 12 hourly without any recurrence of ventricular arrhythmias.

The mechanism of ventricular tachycardia and fibrillation in patients receiving quinidine is thought to be related to prolongation of the relative refractory period of the ventricles whereby a ventricular extrasystole can occur during the vulnerable

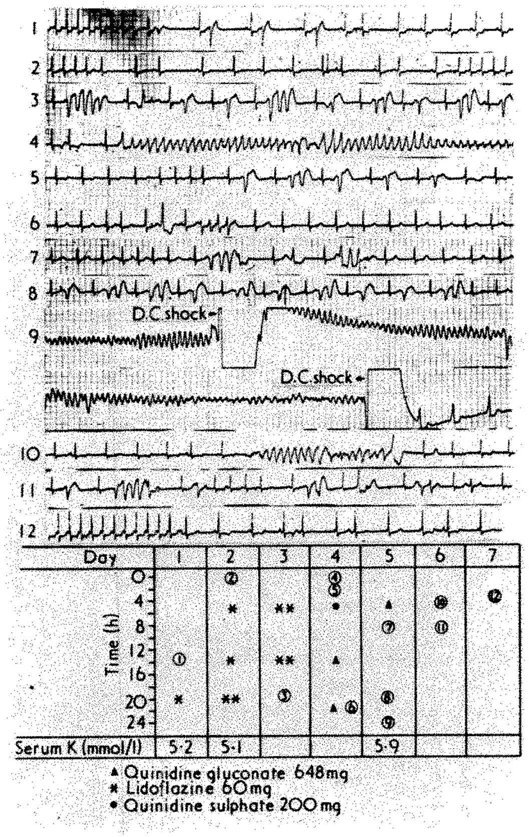

Fig. 2 *Electrocardiograms in patient after institution of lidoflazine and subsequent quinidine therapy. Times and doses of lidoflazine and quinidine are illustrated in relation to rhythm strips. Daily serum potassium levels are recorded.*

period more readily. Lidoflazine, which prolongs the QT interval, may provoke ventricular arrhythmias in similar fashion. Carmeliet and Xhonneux (1971) have shown that the rate of pacemaker activity and depolarisation, the amplitude of the action potential, and the conduction velocity of *in vitro* cardiac muscle are reduced by lidoflazine, while the duration of the action potential and the effective refractory period are prolonged. Lidoflazine may thus be compared to local anaesthetic and other antiarrhythmic drugs such as quinidine. At therapeutic dose levels it does not produce blockade of adrenergic beta receptors. It is believed to interfere directly with the transmembrane conduction processes of electrolytes, particularly calcium and potassium. Where intracellular potassium is diminished and the driving force for repolarising current is lowered lidoflazine may disturb the repolarisation process by further reducing conductance and its use is contraindicated in the presence of hypokalaemia (Batlouni 1970; Carmeliet and Xhonneux, 1971).

In the patient who developed ventricular tachycardia the serum potassium was normal on several occasions and it was previously normal in all 4 patients who subsequently died. The 2 patients who died shortly after starting lidoflazine therapy or shortly after increasing the dosage, however, were both receiving diuretics. Despite potassium supplements and a normal serum potassium level, they may have had an overall total body deficit of potassium.

Therapy with digitalis preparations has been blamed for ventricular arrhythmias in patients receiving lidoflazine. In Batlouni's series (1970), 4 of 18 patients receiving lidoflazine plus digitalis manifested syncope, while only 1 of 32 receiving lidoflazine alone showed this complication. Two patients reported by Miyahara and colleagues (1969) who developed ventricular tachycardia and ventricular fibrillation were both on digitalis, but it is not clear from the report how many of the remaining patients were also receiving digitalis. All 5 of the patients in the report by Piessens and coworkers (1970) who developed ventricular tachycardia, ventricular fibrillation, or sudden death were receiving digitalis, but so were 12 of the remaining 21 who did not develop ventricular tachyarrhythmias. In the series of 30 patients reported by Schlepper and Derro (1972), 21 were on digitalis and of these 15 developed ventricular extrasystoles among whom 5 went on to syncope; none of the 9 patients not receiving digitalis developed ventricular arrhythmias. Czerny *et al.* (1975), however, concluded that digitalis therapy was not related to the occurrence of complicating ventricular arrhythmias in their series of patients. The single patient who showed paroxysmal ventricular tachycardia in that report was receiving only lidoflazine at the time of her arrhythmias, and none of the 4 patients who died was receiving digitalis at the time of their death.

The duration of lidoflazine treatment varied from 8 days to 25 weeks in our 4 patients who died. In 4 of the 6 reported series which describe the time of syncope or ventricular tachyarrhythmias during lidoflazine therapy, the attacks occurred between the first and seventh day after starting treatment. If death were on a similar arrhythmic basis it would seem likely that, as in the case of quinidine syncope or sudden death, it would have occurred within a short time of starting treatment with lidoflazine. The first patient (Case 1) died 8 days after starting therapy and the fourth patient (Case 4) 2½ days after increasing her dosage. It seems reasonable therefore to invoke the drug as possibly being responsible for both these deaths. The other two (Cases 2 and 3), however, died 4 and 25 weeks, respectively, after starting lidoflazine and seem less likely, therefore, to have died from a drug-related arrhythmia.

The nature of the underlying heart disease varied from patient to patient but all 4 patients had intraventricular conduction disturbances including left anterior hemiblock, left bundle-branch block, and non-specific QRS widening. In the report of Piessens and colleagues (1970) only 1 of 5 patients with syncope or sudden death had a conduction disturbance. In the other reports of patients with syncope on lidoflazine it is not clear whether there was a higher incidence of intraventricular conduction disturbances among those experiencing syncope.

An unexplained aspect of the arrhythmogenic potential of lidoflazine is its remarkable safety in the treatment of patients with angina pectoris. In 7 reported series (Verhaeghe, 1969; Batlouni, 1970; Schwalb, 1971; Bernstein and Peretz, 1972; Piessens and De Geest, 1972; Aravanis *et al.*, 1973; Vohra and Sloman, 1973), comprising 247 patients treated with doses equivalent to those used to convert fibrillation, there are no recorded instances of ventricular tachyarrhythmias or syncope. Batlouni (1970) quotes a colleague, however, who treated 2 patients with angina and congestive cardiac failure on digitalis and intensive diuretic treatment with lidoflazine both of whom experienced syncope. In one of these multifocal ventricular extrasystoles were recorded, while in the other ventricular tachycardia was shown subsequent to the syncopal episode. With these 2 exceptions, it is difficult to reconcile the difference in the tendency to ventricular arrhythmias in patients with angina and those with atrial fibrillation treated with lidoflazine.

Analysis revealed a statistical difference with a probability of 8·2 per cent calculated by the exact probability test (Armitage, 1971) in the death rate between the 23 patients receiving quinidine and the group of 28 receiving lidoflazine, including the 14 miscellaneous patients. In view of the fact that the death rate on lidoflazine was approaching the usually accepted statistical significance level of 5 per cent and another patient had sustained dangerous ventricular tachyarrhythmias on lidoflazine therapy, it was decided to terminate the trial. These results, in conjunction with the unacceptably high risk of syncope caused by documented or presumed ventricular tachyarrhythmias in patients receiving lidoflazine for arrhythmias, lead us to the conclusion that it is not an acceptable form of therapy in the treatment or prophylaxis of arrhythmias.

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Pulmonary embolism secondary to anomalies of deep venous system of the leg

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Two cases of recurrent pulmonary emboli secondary to thrombosis in anomalies of the deep veins of the lower limb are presented. In both cases the source of emboli was not evident clinically, and it was only after venography that the venous anomalies were discovered, both being confined to one limb and amenable to surgical intervention. Such anomalies have not previously been reported as sources of venous thromboembolism in adults.

The importance of venography in establishing the source of pulmonary emboli, especially when recurrent, is stressed.

The most common source of pulmonary emboli is leg vein thrombosis (Sevitt, 1965). Numerous factors predispose to thromboembolism including immobilisation after injury, surgery, and in the post-partum period (McIntyre *et al.*, 1972). Varicosities of the superficial veins of the lower limbs may also be associated with thromboembolism (Abramson, 1974). Anomalies of the deep venous system of the lower limb are rare, and 2 cases in which these proved to be the source of recurrent pulmonary embolism are presented.

CASE 1

Five days before admission a 37-year-old woman had suddenly developed retrosternal chest pain while walking. The pain radiated to the left shoulder and back but had no features to suggest a pleuritic or pericardial element and gradually passed off over several hours. Recovery appeared complete apart from some mild lethargy. On the day of admission, after a short period of nausea, the patient noted a fluttering in the chest before collapsing with loss of consciousness for several minutes. There was no significant past or family history and the patient denied taking any drugs.

On admission the patient was pale and clammy with a blood pressure 130/100 mmHg, pulse 100 per minute, temperature 36·8°C and regular respiratory rate of 20 a minute. Cardiovascular examination showed a raised jugular venous pressure of 3 cm, a fourth heart sound, and an ejection systolic murmur along the left sternal edge. Fine inspiratory crepitations were present at both lung bases and mild bilateral ankle oedema was present. The pulmonary component of the second heart sound did not appear increased and no abnormality was detected in the abdomen. The lower limbs appeared normal with no evidence of venous thrombosis, varicose veins, or vascular bruits. Chest radiograph was normal and electrocardiogram showed a normal frontal axis with non-diagnostic ST-T changes inferolaterally.

As myocardial ischaemia or infarction was considered possible, she was monitored in the coronary care unit. No anticoagulants were given and serial electrocardiograms from the 2nd to 8th days showed evolving T wave inversion inferiorly and over all the praecordial leads. Apart from an initially raised lactic dehydrogenase of 516 IU/l (normal < 470) all enzymes were normal. On the 3rd day a chest radiograph showed the development of an area of opacification in the lateral segment of the right upper lung suggestive of a pulmonary infarct.

Technetium-99-macroaggregated ferrous hydroxide (MAFH) lung scintigram (Fig. 1) showed perfusion defects in both midzones, right apex, and right base, consistent with pulmonary emboli. Shortly after the lung scintigram, the patient had a respiratory arrest with an associated junctional rhythm at a rate of 65 beats a minute. After resuscitation a loud fourth heart sound with an associated right ventricular impulse was noted. The patient was started on full anticoagulation with intravenous heparin and her condition rapidly stabilised. Bilateral lower limb venography was

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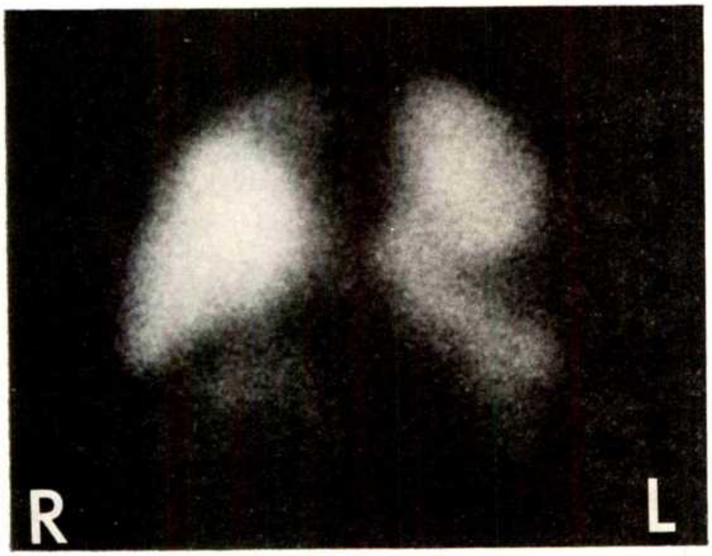

Fig. 1 *Lung scintigram in case 1 showing perfusion defects at apex midzone and base of right lung and midzone of left lung.*

performed and showed an aneurysmal varix of the right popliteal vein with a filling defect within the varix suggestive of thombus (Fig. 2). Venograph of the left leg was normal.

The next day the popliteal vein was explored under general anaesthesia and an aneurysmal varix was exposed and found to have no arterial connections. The varix was opened, a large thrombus removed, and the varix excised. The defect in the popliteal vein was closed by direct suture. After operation she was maintained on full heparinisation with a calf stimulator being applied to the leg to maintain a high venous flow. Venography was repeated 24 hours later and at the adductor canal showed some compression of the popliteal vein lumen which was thought to be the result of a wound haematoma.

Further venography was performed 10 days after operation because of persistent pain and oedema of the leg. This showed complete obstruction of the deep venous system of the right leg. An inferior venocavogram showed no extension of thrombus beyond the femoral vein. The patient was discharged 3 weeks after operation on oral anticoagulants and full length elastic stockings for persistent leg oedema. Repeat lung scan 3 months later was normal and at 12 months follow-up she remains well with no recurrence of pulmonary emboli.

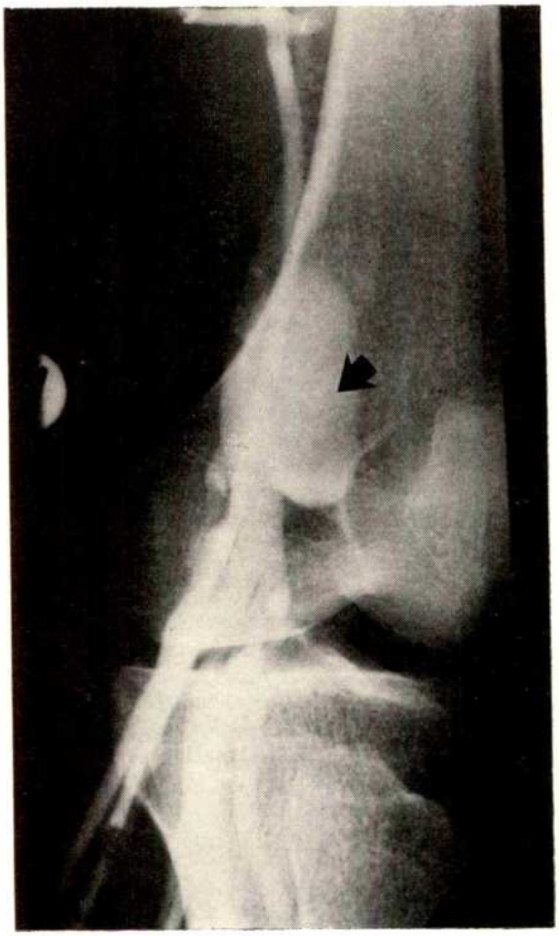

Fig. 2 *Venogram of right leg in case 1 showing an aneurysmal varix of the popliteal vein with intraluminal filling defect (arrow).*

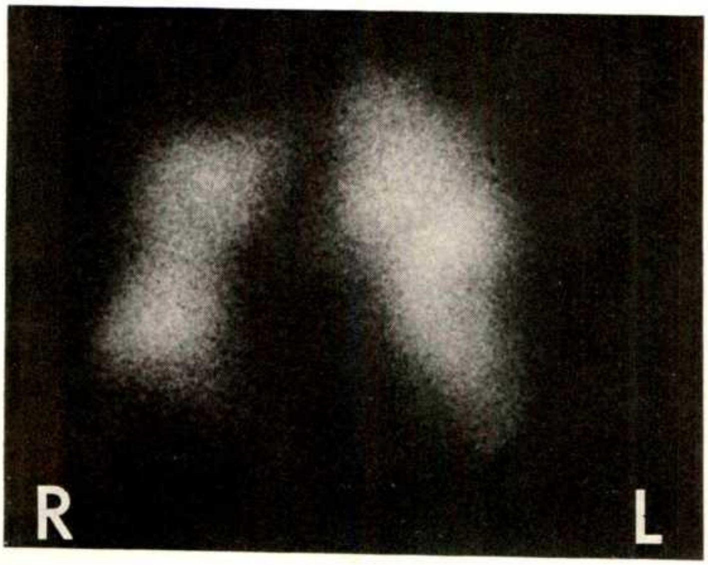

Fig. 3 *Lung scintigram in case 2 showing multiple perfusion defects in both lung fields.*

CASE 2

A 62-year-old man was referred from another hospital with a 7-month history of progressive effort dyspnoea and recurrent palpitations. Atrial tachycardia had been documented on two occasions. Occasional chest tightness had occurred and for 2 months ankle oedema and abdominal swelling had been noted. His past history included an admission to a country base hospital 10 years previously, with a diagnosis of myocardial infarction said to be complicated by venous thrombosis. The records of this admission were unavailable; however, the patient recalls being dyspnoeic at the time but without chest pain.

Physical examination revealed a patient in no distress with findings of pulmonary hypertension. He had a raised jugular venous pressure (2 cm) with a prominent 'a' wave, a right ventricular lift, and a loud pulmonary component of the second heart sound. There was a pansystolic murmur audible at at lower left sternal edge which increased on inspiration and was consistent with tricuspid regurgitation. Two centimetres of non-pulsatile liver was palpable and his chest was clinically clear. Examination of the legs showed no venous abnormalities or bruits.

A chest *x*-ray film showed cardiomegaly with prominent pulmonary arteries suggesting pulmonary hypertension. An electrocardiogram showed sinus rhythm with right axis deviation of +110°, right atrial enlargement, clockwise rotation, and digoxin effect. A lung scintigram with Technetium 99 MAFH showed multiple perfusion defects (Fig. 3). An echocardiogram showed a large right ventricle with a prominent B wave on the tricuspid valve suggesting raised end-diastolic right ventricular pressure with the left ventricle, mitral valve, and aortic valve being normal. Bilateral venography of the lower limbs showed a large varix consisting of numerous small venous channels at the junction of the left femoral and popliteal veins (Fig. 4A). The right leg was normal. The varix contained multiple filling defects thought to be thrombus. Right heart catheterisation (Table) showed pronounced pulmonary hypertension and pulmonary angiography showed multiple filling defects predominantly in the right lung consistent with emboli (Fig. 5).

Table *Results of cardiac catheterisation*

Site	*Pressure (mmHg)*	*Mean pressure (mmHg)*
Right atrium	a 13 v 9	6
Right ventricle	90/0 (15)	
Pulmonary artery	90/39	53

In view of the extensive nature of the venous anomaly it was decided to ligate the right femoral vein distal to its junction with the long saphenous vein. The patient was maintained on oral anticoagulants and when reviewed 12 months later had shown no improvement. There were signs of persistent pulmonary hypertension and tricuspid regurgitation. Repeat lung scintigram was unchanged. Right heart catheterisation showed a rise in pulmonary artery pressure at 92/46 mmHg.

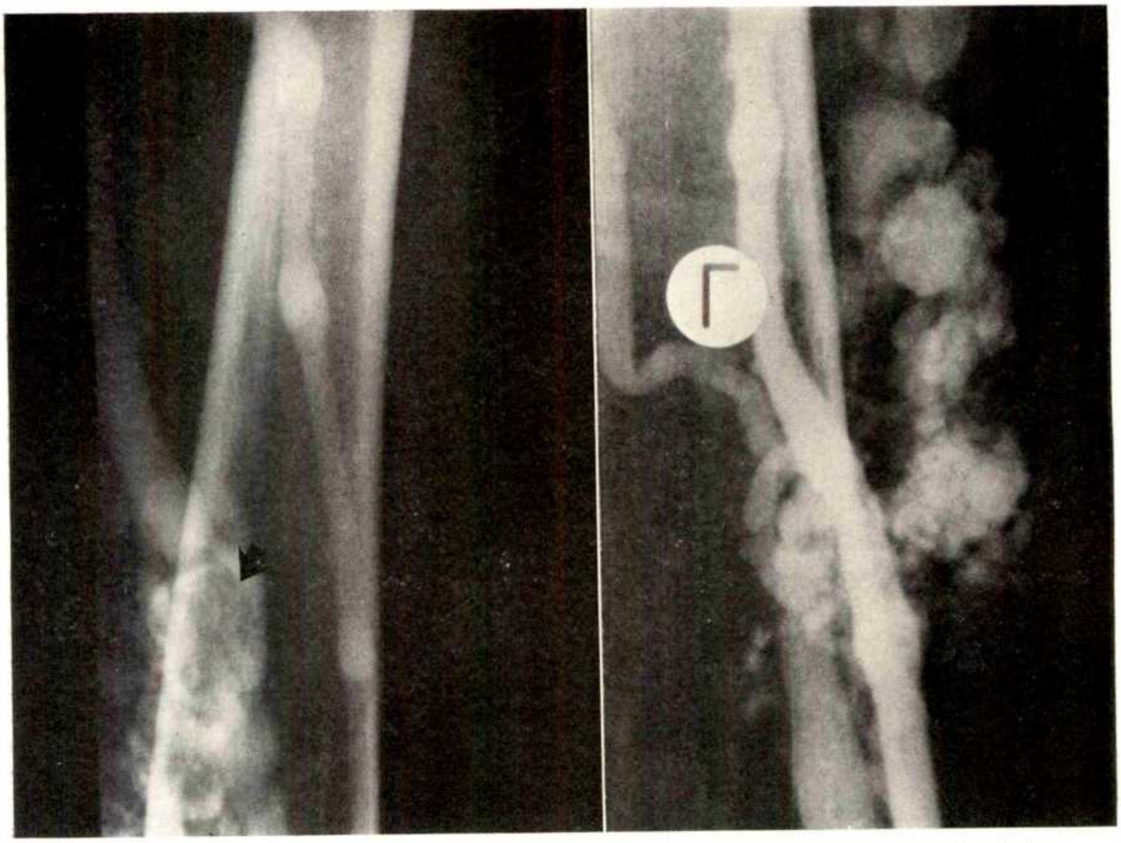

Fig. 4 *Venograms of left leg in case 2. (A) The venous angioma with negative shadows suggests intraluminal filling defects (arrow). (B) The repeat venogram 12 months later shows no filling defects within the angioma.*

Right atrial pressure had increased, with a mean pressure of 19 mmHg. Repeat venography showed opacification of the venous malformation with no filling defects present (Fig. 4B). However, there was interruption to flow in the femoral vein proximally at the site of previous ligation. It was felt that no further surgical procedure was indicated and he was discharged on long-term anticoagulants and anti-failure therapy.

Discussion

Both cases presented with problems associated with pulmonary thromboembolism and were found to have underlying deep venous anomalies which were unsuspected clinically. The first patient presented after an episode of acute thromboembolism which was initially misdiagnosed as an episode of myocardial ischaemia. Chest x-ray changes suggested pulmonary infarction and lung scintigram strongly supported pulmonary embolism. Clinical examination gave no clue as to the origin of the emboli and the aneurysmal varix of the right popliteal vein was only discovered as a result of bilateral venography.

The second patient presented a problem of pulmonary hypertension and right heart failure secondary to chronic pulmonary embolism. The history possibly dated back 10 years to when he was thought to have had a myocardial infarct. In this patient pulmonary embolism was confirmed on lung scintigram and pulmonary angiography, with pronounced pulmonary hypertension being present at right heart catheterisation. Again the underlying deep venous varix of the left leg was unsuspected clinically and was only discovered at venography.

Pure venous dysplasias of the extremities are rare and are usually unilateral (Browse, 1973). Malan and Puglionisi (1964) discuss the possible aetiology of pure venous dysplasias and suggest a classification into four main groups: (i) phlebectasia, (ii) phlebangiomas, (iii) phlebangiomatosis; and (iv) a mixed group. Their classification is an extensive one

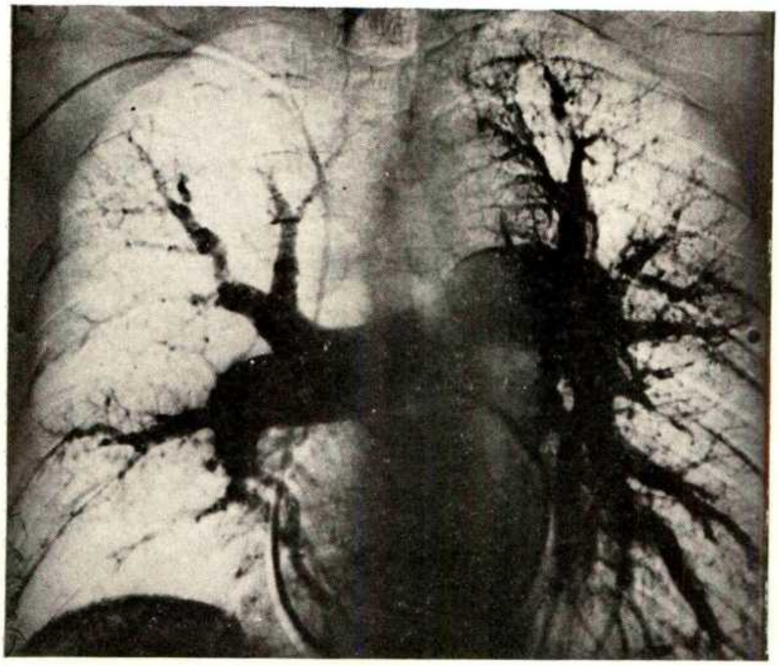

Fig. 5 *Pulmonary angiogram in case 2 showing extensive perfusion defects in both lung fields.*

but in essence phlebectasia refers to a congenital dilatation of the venous tree of a limb which may be regional or diffuse. Phlebangiomata are limited venous hamartomata with a cavernous and capillary structure. When these venous hamartomata are extensive or multicentred they are called phlebangiomatosis. Associations between the previous three groups constitute the mixed group. They described 21 cases, but in all patients an abnormality of the superficial venous system was present. In 1971 Lea Thomas and Andress described angiographic techniques in venous dysplasias and attempted to simplify the classification on a radiological basis into two main groups. Venous angioma referred to lesions which consist mainly of cavernous spaces while phlebectasia described lesions in which the principal abnormality was dilatation of the venous trunk. They described 16 cases, but again all had superficial venous abnormalities. This makes classification of our cases difficult, since in both there was a localised lesion in the deep venous system with no abnormality of the superficial venous system. Using Lea Thomas and Andress's classification our first patient's lesion most closely resembles a localised phlebectasia and our second patient's lesion a venous angioma.

To our knowledge pulmonary embolism secondary to unsuspected venous anomalies of the deep veins of the lower limb has not previously been described in adults. Maszkiewitz in 1973 did, however, describe a case of a newborn infant who succumbed to pulmonary embolism from thrombi originating from a hypoplastic femoral vein.

Venous thromboembolism constitutes an important cause of morbidity and mortality and several techniques have been developed to aid in the diagnosis. Kakkar in a recent review (1975) stresses the importance of venography as being the single most useful investigation in the diagnosis of suspected thrombosis. It not only helps in outlining the exact site and extent of the thrombus but aids in the decision about subsequent therapy. Other tests such as ^{125}I fibrinogen scanning, ultrasound, and plethysmography have been useful as screening tests but would have been of no use in defining accurately the source of embolism in our 2 cases. Venography on the other hand accurately outlined the previously unsuspected venous anomalies and allowed a decision to be made about surgical treatment. In our first case the aneurysmal varix was unilateral and appeared readily suitable for local surgical excision. The defect was closed by direct suture but in view of the narrowing on repeat venography and subsequent secondary thrombosis the use of a vein patch to close the defect or alternatively proximal femoral vein ligation might have prevented this complication. In the second case venography indicated an extensive deep venous varix which was unsuitable for local venous reconstruction and it was decided to ligate the deep femoral vein just distal to the origin of the long saphenous vein. This patient's pulmonary hypertension remained unchanged when reviewed 12 months after surgery.

Our 2 cases demonstrate an unusual cause for recurrent pulmonary emboli and emphasise the importance of venography in investigation of this problem.

We thank Dr. J. M. Gardiner for referring our first case and Drs. H. Luke and L. Dugdale for the radiological and isotope imaging studies.

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Recurrent pulmonary embolism due to hydatid disease of heart

Study of 3 cases, one with intermittent tricuspid valve obstruction (atrial pseudomyxoma)

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Three cases of pulmonary hypertension caused by hydatid emboli from the right side of the heart are described; cardiac catheterisation was performed in 2. One case was confirmed at operation and 2 at necropsy. The pulmonary emboli were caused by hydatid vesicles in all 3 cases and in none was there pulmonary thrombosis; free scolices were found in the pulmonary alveoli in 2. In 1 patient with repeated syncopal attacks there was a pedunculated cyst in the right atrium which was thought to have intermittently obstructed the tricuspid valve. Gamma radiography, angiocardiography, and necropsy suggested a mechanical cause for the pulmonary hypertension with no vasoconstrictive element. The surgical patient was alive and well 18 months later.

Involvement of the heart in hydatid disease occurs in about 0·5 to 2·0 per cent of cases, and of the right side of the heart in about one-quarter of these (Dévé, 1946; Artucio *et al.*, 1962; Di Bello *et al.*, 1968, 1970). Hydatid embolism has rarely been reported. Three cases are described in which this diagnosis was made during life; 1 was operated on successfully and 2 were confirmed at necropsy. The clinical features are summarised in the Table.

Case reports

CASE 1

A 29-year-old man gave a one-month history of pleuritic pain, first on the left side of the chest and then on the right. In the chest *x*-ray (Fig. 1) there was a rounded prominence of the left cardiac border which was less opaque in its outer zone. In the right lung base there was a diffuse round shadow which had disappeared 15 days later. The electrocardiogram showed right axis deviation and T wave inversion in leads I and aVL, and a praecordiogram recorded a systolic lift to the left of the sternum. Cardiac catheterisation indicated pulmonary hypertension (44/30 mmHg). Right ventricular angiography showed a bulge of the upper part of the interventricular septum with a mobile projection into the outflow tract, and a round shadow in the lower branch of the left pulmonary artery. Coronary arteriography showed an arched displacement of the anterior descending coronary artery.

The deformity of the cardiac outline and the finding of 13 per cent eosinophils in the blood suggested the diagnosis of a hydatid cyst. The Casoni test was positive. The existence of pulmonary hypertension and the angiographic appearance suggested that the cyst was in the upper part of the septum and had perforated into the right ventricle.

Using cardiopulmonary bypass and a medial sternotomy the right ventricle was opened by a transverse incision. A cyst was found in the septum with vesicles in the right ventricle and pulmonary artery (Fig. 2). The contents of these were aspirated and the cyst membrane was excised. Eighteen months later the patient was alive and well, the chest *x*-ray was normal; the electrocardiogram showed evidence of septal necrosis.

CASE 2

A 63-year-old man gave a one-year history of increasing breathlessness, occasional pain in the right chest, a dry cough, and occasional haemoptysis. For 5 months he had had recurrent syncopal attacks without convulsions lasting for 2 or 3 minutes. These attacks were not related to coughing or to postural changes. At first they occurred only once or twice a month, but in the previous 20 days they happened once or twice a day.

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Table *Clinical features in 3 cases of cardiac hydatidosis*

	Case 1	*Case 2*	*Case 3*
Age (y)	29	63	32
Sex	M	M	F
Time of evolution	1 month	1 year	4 years
Symptoms	Costal pain	Progressive dyspnoea; syncopal episodes; haemoptysis	Progressive dyspnoea; haemoptysis
Eosinophils	13%	—	7%
Electrocardiogram	Right axis deviation	Right axis deviation; anteroseptal necrosis; injury current	Right axis deviation; right ventricular hypertrophy and systolic overload
Pulmonary pressure (mmHg)	44/30	—	69/26
Deformity of cardiac outline	Yes	Yes	—
Location	Right ventricle	Right atrium and right ventricle	Both ventricles
Confirmation	Surgery	Necropsy	Necropsy

The chest *x*-ray film (Fig. 3) showed multiple round cystic shadows in the lung fields, and there was a rounded prominence of the right cardiac border in the position of the right atrium. The electrocardiogram showed right ventricular preponderance and evidence of anteroseptal necrosis with an injury pattern.

Eight days later he developed left upper lobe pneumonia caused by a streptococcal infection from which he died.

The clinical diagnosis of hepatic, pulmonary, and probably cardiac hydatid cysts was confirmed at necropsy. A cyst 1·5 cm in diameter was found in the anterior wall of the right ventricle. Another large cyst occupied the right atrium with a pedunculated mass almost occluding the tricuspid valve (Fig. 4). Medium-sized pulmonary arteries were occluded by hydatid vesicles.

Microscopy of the pedunculated mass in the right atrium showed it to consist of hydatid membranes and organising blood clots. Section of the lungs revealed multiple cysts and some free scolices in the alveoli. Some pulmonary arteries were occluded by vesicles but there was no arterial thrombosis. Macroscopical and microscopical studies of the brain were normal.

There seems little doubt that the fainting episodes were caused by the pedunculated hydatid body in the right atrium intermittently occluding the tricuspid valve as may happen with an atrial myxoma.

CASE 3

A 33-year-old woman was operated on for a hydatid cyst 6 years peviously. Two years later she began to be breathless on exertion and to have asthmatic attacks. She also had two attacks of urticaria. She had acrocyanosis, and there were 7 per cent eosinophils in the leucocyte count.

The *x*-ray film of the chest (Fig. 5) showed an enlarged heart with prominence of the pulmonary artery, and two small cysts in the left lung. The electrocardiogram (Fig. 6) showed right axis deviation and incomplete right bundle-branch block. It suggested right atrial enlargement and right ventricular hypertrophy with systolic overload. Gamma radiography of the lungs showed severe perfusion defects in the right upper and left lower zones.

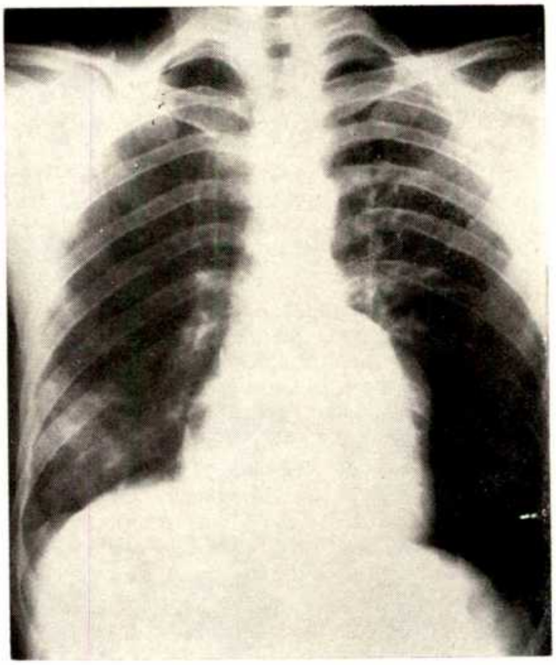

Fig. 1 *Case 1. Chest x-ray film showing rounded prominence of left cardiac border, and a diffuse round shadow in the right base.*

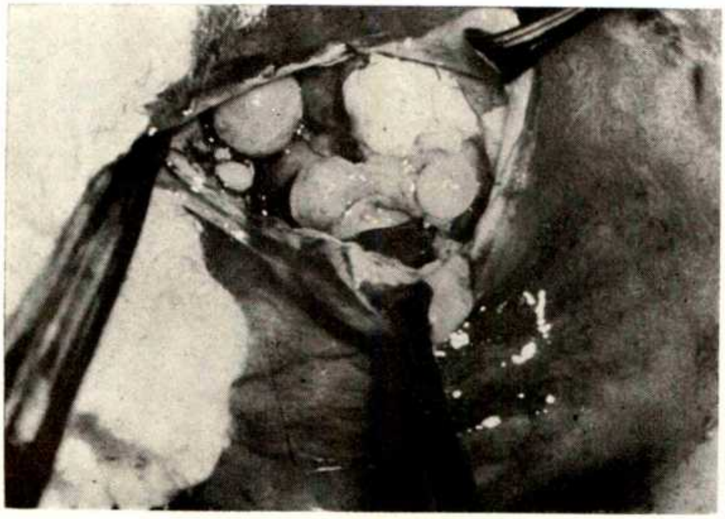

Fig. 2 *Case 1. Opened hydatid cyst occupying upper part of the interventricular septum and anterior wall of right ventricle. Several vesicles (daughter cysts) and the hydatid membrane are visible.*

At cardiac catheterisation the pulmonary arterial pressure was 69/26 mmHg. Pulmonary angiography (Fig. 7) showed dilatation of the pulmonary trunk and its main branches. The right upper lobe branch was occluded 1 cm from its origin and the inferior lobe branches were tortuous and irregular. There was an extensive avascular zone in the left lower lobe.

The patient died suddenly. At necropsy there was a hydatid cyst in the interventricular septum with several vesicles protruding into the right ventricle (Fig. 8). A cyst had also perforated into the left

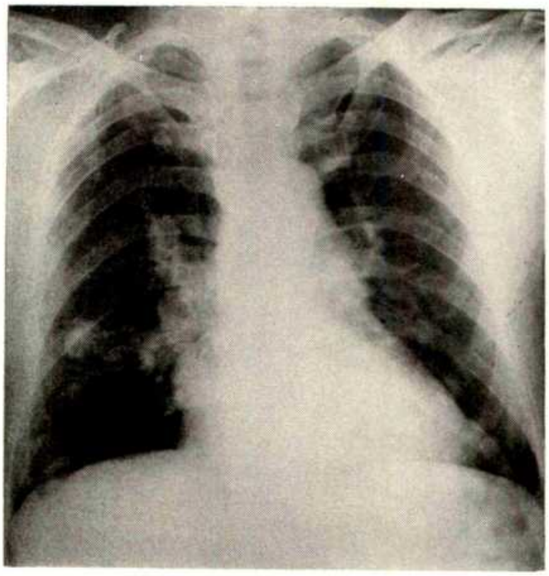

Fig. 3 *Case 2. Check x-ray film showing a rounded prominence of the right cardiac border. Round cystic shadows in both lung fields.*

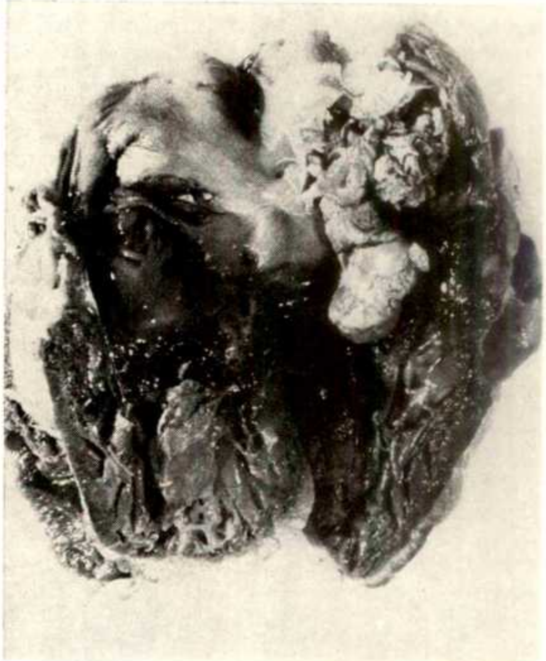

Fig. 4 *Case 2. The opened heart showing a large cyst in the right atrium with a pedunculated portion passing through the tricuspid valve into the right ventricle.*

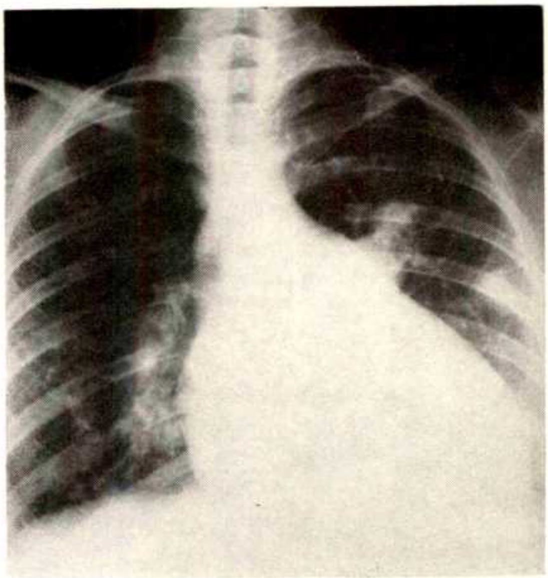

Fig. 5 *Case 3. Chest x-ray film showing enlargement of the heart with prominent main pulmonary artery, and two small cysts in the left lung.*

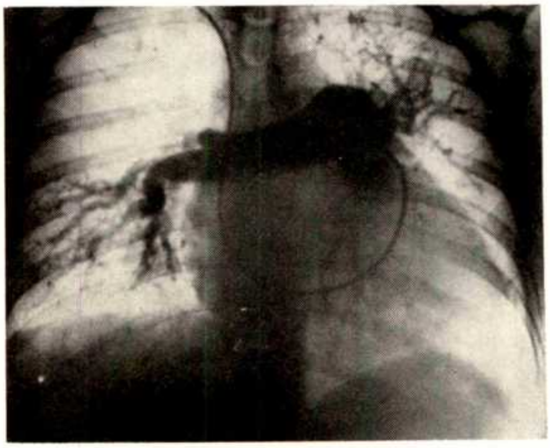

Fig. 7 *Case 3. Pulmonary angiogram showing dilated pulmonary trunk, occlusion of the right upper lobe branch with tortuous lower lobe vessels, and avascular left lower zone.*

ventricle. Both lungs showed multiple arterial emboli caused by hydatid vesicles and free scolices, with recent areas of infarction but no arterial thrombosis. There were in addition three small cysts in the left lung, and aortic, common iliac, renal, and thyroid hydatid cysts were also found.

The history together with *x*-ray film, electrocardiogram, catheterisation, and angiographic data, aided by the gamma scan, suggested hydatid disease of the heart with multiple pulmonary embolism. Massive embolism caused sudden death before operation could be undertaken.

Discussion

Echinococcosis of the heart is usually associated with pulmonary or hepatic hydatidosis. One of these cases however (Case 1) presented as a solitary cardiac hydatid cyst. The heart muscle is an unfavourable site for the development of a cyst as the

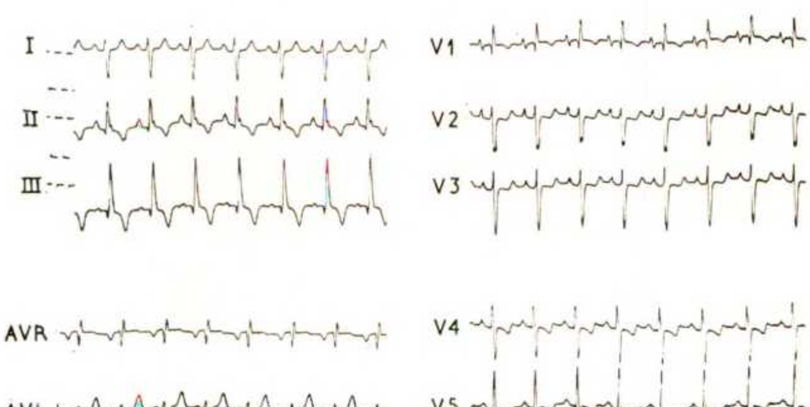

Fig. 6 *Case 3. Electrocardiogram showing right axis deviation and incomplete right bundle-branch block.*

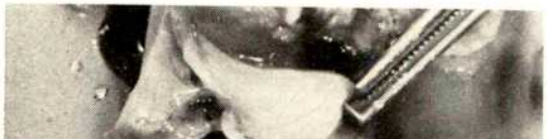

Fig. 8 *Case 3. The opened heart showing a hydatid cyst in the interventricular septum with vesicles and membrane protruding into the right ventricle.*

contraction of the heart compresses it intermittently and shortens its life; it is of importance prognostically, as it renders it liable to rupture either into the cavity of the heart or into the pericardium.

The embryo reaches the heart muscle by way of the coronary circulation and not directly from the cardiac cavity. Usually the embryos from ingested ova cross the intestinal wall to reach the portal or azygos vein. Those that are not arrested in the liver reach the right atrium and right ventricle and pass by way of the pulmonary artery and pulmonary vein to the left side of the heart, whence they reach the coronary circulation. Occasionally a pulmonary cyst may rupture into a pulmonary vein liberating scolices into the blood flowing to the left ventricle, aorta, and coronary arteries. Once in the myocardium and subject to continuous 'trauma' the cyst may grow, or calcify and die. A developing cyst is liable to rupture into the cavities of the heart, producing pulmonary embolism if into the right ventricle and systemic embolism if into the left; or it may rupture into the pericardium producing a pericardial effusion (Gibson, 1964), or later constriction (Heyat *et al.*, 1971). Usually there is an asymptomatic period of one to five years, or even longer, before these complications occur (Ivanissevich and Rivas, 1962).

The diagnosis of cardiac hydatidosis is based on the clinical and electrocardiographic findings, and especially the radiological appearances, particularly when associated with cysts elsewhere, eosinophilia, and a positive Casoni test. Nevertheless the majority of cases which have been described were unsuspected necropsy or surgical findings because attention is usually concentrated on hepatic or pulmonary cysts. If there is a bulge of the cardiac outline of non-homogeneous density which is not accounted for by valvular disease, cardiac hydatidosis should be considered, and a diagnostic cardiac catheterisation with angiography performed.

Purriel and his colleagues (1970) reviewed 39 published cases of hydatid pulmonary embolism and added 4 cases of their own. Further cases have been published since including 2 by Perez-Gomez *et al.* (1973). Most authors classify hydatid pulmonary embolism in 3 groups:

(a) acute fatal cases,
(b) subacute pulmonary hypertension with death in less than a year,
(c) chronic pulmonary hypertensive cases.

The majority of cases appear to follow a course of prolonged pulmonary hypertension punctuated by acute embolic episodes. In our 3 cases the clinical symptoms of pulmonary hypertension were present for 1 month, 1 year, and 4 years, respectively.

The prognosis of hydatid pulmonary embolism is grave, and only one case, that of Artucio *et al.* (1962), had a survival time measured in years before operation. Our case 1 appears to be the second to be cured by operation.

The angiographic, and particularly the surgical and necropsy findings, show that the pulmonary emboli are caused by vesicles or daughter cysts, and by scolices, and in none of our cases was there blood clot or added thrombosis. The smooth-walled daughter cysts appear to act purely mechanically by blocking the blood flow and not by irritating the vascular endothelium. In case 3 the lung scan showed perfusion defects affecting the right upper and left lower lobes which the patient tolerated surprisingly well until he died some days later of a massive embolism. It seems that hydatid embolism produces very little pulmonary vasoconstriction and that the haemodynamic effect depends on the number and size of the occluded vessels. Only 2 cases, an exceptional one of Dévé (1946) and one of Perez-Gomez *et al.*, were associated with a thrombus.

Purriel *et al.* (1970) and other authors have commented on the protrusion of hydatid cysts into the cardiac cavities with the possibility of intermittently blocking a valve orifice, and syncope has been re: ported in some cases. Our case 2 is noteworthy in this respect in that he presented with repeated syncopal attacks and was found to have a pedunculated hydatid cyst protruding into the right atrium which we suspect was intermittently obstructing the tricuspid valve in the same way as is seen with a myxoma in this cavity.

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Physiological responses to prompt and sustained squatting[1]

Measurement by systolic time intervals

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Ten healthy men, ages 22 to 35, were studied non-invasively standing (control), at the onset of squatting ('prompt squat'), and at two minutes of squatting. Squatting produced decreases in heart rate, isovolumic contraction time, pre-ejection period, and pulse transmission time, and increases in the time from onset of depolarisation to the first heart sound, left ventricular ejection time, and the ejection time index. These results of systolic time intervals are consistent with the bradycardia and increased ventricular filling induced by squatting. Major changes from control measurements were found at the onset of squatting, showing the impact of prompt squat on left ventricular performance.

Prompt squat, a simple non-invasive challenge which acutely increases venous return, stroke volume, and systemic arterial pressure, has been applied in diagnosing obstructive cardiomyopathy, intracardiac shunts, and variants of the click-murmur syndrome. A variety of haemodynamic measurements have been made in both normal subjects and patients with appropriate findings, while non-invasive cardiography during squatting has been confined to phonocardiography of murmurs (O'Donnell and McIlroy, 1962; Nellen *et al.*, 1967, 1968; Fontana *et al.*, 1975).

The purpose of this investigation was to define the physiological effects of prompt and sustained squatting as expressed by changes in systolic time intervals and to compare the responses with the established haemodynamic consequences of squatting.

Subjects and methods

Ten healthy men, ages 22 to 35, volunteered for this study. A normal electrocardiogram, chest *x*-ray, medical history, and physical examination, together with signed informed consent were prerequisites for participation in the investigation.

Subjects entered the laboratory in the morning in the post-absorptive state. After application of the external electrodes and microphones, subjects were given a 20-minute supine rest period.

RECORDINGS

Tracings were recorded on an 8-channel Hewlett Packard optical recorder No. 568–100A and included a simultaneous electrocardiogram, phonocardiogram, and carotid pulse curve (Spodick and Quarry-Pigott, 1973).

Three sequential recordings were made on each subject: (1) during standing (2 minutes after the subject stood up), (2) onset of squatting ('prompt squat'), and (3) at 2 minutes of squatting ('sustained squat').

BLINDING

To prevent observer bias, measurements were made separately and without knowledge of the results of the other recordings for each subject.

MEASUREMENTS

Five beats were measured on each of the 3 recordings for each subject. Time was measured from the 'q' wave on the electrocardiogram (zero point for all measurements) to the mitral component of the first heart sound ($q\text{–}I_m$), the second heart sound (II_A), the carotid upstroke (CAR_u), and the carotid incisura (CAR_{in}). The preceding RR interval of each beat measured was also determined. Heart rate and systolic time intervals were calculated from these points as previously described (Spodick and Quarry-Pigott, 1973).

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STATISTICAL ANALYSIS

The mean values of the 5 beats measured for each subject during each of the 3 conditions (standing control, prompt squat, and sustained squat) were analysed.

The t test for paired comparisons was used to compare standing vs. onset of squatting, standing vs. 2 minutes of squatting, and onset of squatting vs. 2 minutes of squatting.

Results

Results are summarised in Tables 1 and 2.

Table 1 *Effects of prompt and sustained squatting*

		Standing	*Squat onset*	*Squat 2 min*
HR				
	$\bar{x}$	76·2	69·8	62·0
	SD	± 9·24	± 6·16	± 4·11
	SE	± 2·92	± 1·95	± 1·30
$q\text{-}I_m$				
	$\bar{x}$	58·3	66·8	67·0
	SD	± 5·14	± 10·04	± 12·25
	SE	± 1·63	± 3·18	± 3·87
IVCT				
	$\bar{x}$	81·8	47·9	60·3
	SD	± 5·47	± 12·78	± 9·72
	SE	± 1·73	± 4·04	± 3·07
PEP				
	$\bar{x}$	140·1	114·7	127·3
	SD	± 7·68	± 10·13	± 9·27
	SE	± 2·43	± 3·20	± 2·93
LVET				
	$\bar{x}$	232·2	277·8	290·1
	SD	± 19·79	± 19·05	± 14·98
	SE	± 6·26	± 6·02	± 4·74
ETI				
	$\bar{x}$	323·7	361·6	364·5
	SD	± 11·47	± 16·65	± 13·88
	SE	± 3·63	± 5·27	± 4·39
PEP/LVET				
	$\bar{x}$	0·607	0·414	0·441
	SD	± 0·0598	± 0·0414	± 0·0407
	SE	± 0·0189	± 0·0131	± 0·0129
PTT				
	$\bar{x}$	39·3	37·8	35·0
	SD	± 7·56	± 5·69	± 7·10
	SE	± 2·39	± 1·80	± 2·25

HEART RATE (FIGURE)

Subjects showed a mean, statistically insignificant, decrease in heart rate of −6·4 beats per minute at the onset of squatting (standing vs. onset squat: $P > 0{\cdot}05$). Individual changes varied; e.g. 2 subjects had large rate reductions of −21 and −24 beats respectively, 3 subjects showed a decrease of only 1 beat per minute, 1 subject had no change, and another showed an increase of 4 beats per minute. However, when standing heart rate was compared with sustained squatting, uniform decreases resulted among all 10 subjects (mean decrease of −14·2 beats per minute; $P < 0{\cdot}001$). This uniform decrease in heart rate was also apparent when prompt squat was compared to 2 minutes of squatting (mean decrease of −7·8 beats per minute; $P < 0{\cdot}002$).

Table 2 *Comparison between values observed standing, at onset of squatting, and after squatting at 2 minutes*

		Standing vs squat onset	*Standing vs squat 2 min*	*Squat onset vs squat 2 min*
HR				
	mean Δ	− 6·4	− 14·2	− 7·8
	T	− 2·1624	− 4·7880	− 4·6284
	P	> 0·05	< 0·001	< 0·002
$q\text{-}I_m$				
	mean Δ	+ 8·5	+ 8·7	+ 0·2
	T	2·5071	2·0318	0·0700
	P	< 0·05	> 0·05	> 0·8
IVCT				
	mean Δ	− 33·9	− 21·5	+ 12·4
	T	− 7·0671	− 5·1866	3·5789
	P	< 0·001	< 0·001	< 0·01
PEP				
	mean Δ	− 25·4	− 12·8	+ 12·6
	T	− 9·5072	− 5·7142	4·0751
	P	< 0·001	< 0·001	< 0·005
LVET				
	mean Δ	+ 45·6	+ 57·9	+ 12·3
	T	15·8770	16·6458	5·9852
	P	< 0·001	< 0·001	< 0·001
ETI				
	mean Δ	+ 37·9	+ 40·8	+ 2·9
	T	11·0181	16·6627	1·7800
	P	< 0·001	< 0·001	> 0·1
PEP/LVET				
	mean Δ	− 0·193	− 0·166	+ 0·027
	T	− 10·8248	− 12·7567	2·5350
	P	< 0·001	< 0·001	< 0·05
PTT				
	mean Δ	− 1·5	− 4·3	− 2·8
	T	− 0·8527	− 5·0952	− 1·6813
	P	> 0·2	< 0·001	> 0·1

Q-I m

The initial increase in $q\text{-}I_m$ from standing to onset of squatting was statistically significant ($P < 0{\cdot}05$) while the comparison of standing vs. squatting at 2 minutes was not ($P > 0{\cdot}05$). The actual differences among these comparisons, however, are very small: the mean increase for standing vs. onset of squatting was +8·5 ms ($t = 2{\cdot}5071$) while the mean increase for standing vs. 2 minutes of squatting was +8·7 ms ($t = 2{\cdot}0318$). In both cases 2 of the 10 subjects showed decreases in $q\text{-}I_m$ while 8 showed increases. The scatter, however, was greater for standing vs. 2 minutes of squatting. The comparison of $q\text{-}I_m$ at the onset of squatting vs. 2 minutes of squatting, showed no difference ($P > 0{\cdot}8$).

ISOVOLUMIC CONTRACTION TIME

All comparisons were statistically significant and all subjects uniformly showed changes in the direction of the mean change with only one exception (i.e. 9 subjects showed decreases in isovolumic contraction time from standing to 2 minutes of squatting, but 1 subject showed a small increase of +2 ms).

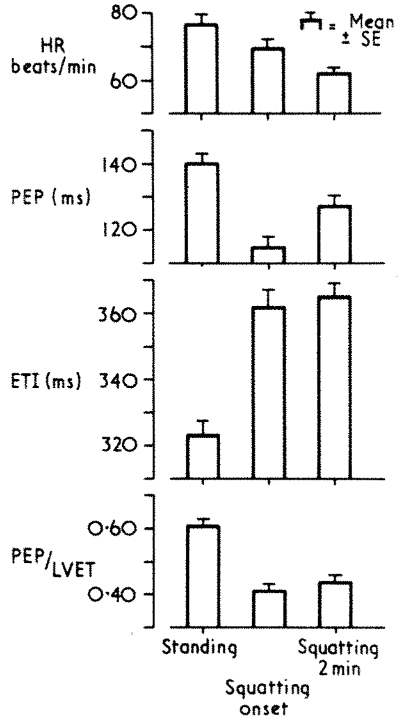

Fig. *Changes in principal measurements from standing control to prompt and sustained squatting. HR = heart rate. PEP = pre-ejection period. ETI = ejection time index. PEP/LVET = ratio of pre-ejection period to left ventricular ejection time.*

The mean decrease in isovolumic contraction time from standing to onset of squatting was –33·9 ms ($P < 0{\cdot}001$); the mean decrease from standing to 2 minutes of squatting was –21·5 ms ($P < 0{\cdot}001$); the mean increase from onset of squatting to 2 minutes of squatting was +12·4 ms ($P < 0{\cdot}01$).

PRE-EJECTION PERIOD (PEP) (FIGURE)
All comparisons for pre-ejection period were statistically significant and all but one subject showed directional changes which were consistent with the mean change (the one exceptional subject showed no change from onset to two minutes of squatting). The mean decrease from standing to onset of squatting was –25·4 ms ($P < 0{\cdot}001$); the mean decrease from standing to 2 minutes of squatting was –12·8 ms ($P < 0{\cdot}001$); the mean increase from onset to 2 minutes of squatting was +12·6 ms ($P < 0{\cdot}005$).

LEFT VENTRICULAR EJECTION TIME (LVET)
Left ventricular ejection time progressively increased from standing to onset of squatting to 2 minutes of squatting. All subjects, without exception, showed increased ejection time and all comparisons were statistically significant ($P < 0{\cdot}001$): the mean increase from standing to onset of squatting was +45·6 ms; from standing to squatting at 2 minutes was +57·9 ms; from onset to 2 minutes of squatting was ±12·3 ms.

EJECTION TIME INDEX (FIGURE)
When left ventricular ejection time was corrected for heart rate, the results show uniformly significant increases for standing vs. onset of squatting (mean increase +37·9 ms; $P < 0{\cdot}001$) and for standing vs. 2 minutes of squatting (mean increase +40·8 ms; $P < 0{\cdot}001$). The comparison of onset of squatting vs. 2 minutes of squatting showed no significant difference (mean change +2·9 ms; $P > 0{\cdot}1$—with individual changes ranging from +10 to –7 ms).

PEP/LVET (FIGURE)
All subjects showed decreases in PEP/LVET for standing vs. onset of squatting (mean decrease –0·193; $P < 0{\cdot}001$) and for standing vs. 2 minutes of squatting (mean decrease –0·166; $P < 0{\cdot}001$). The small difference (+0·027) between onset of squatting and 2 minutes of squatting was less significant ($P < 0{\cdot}05$); here 6 subjects showed increases ranging from +0·02 to +0·08, 2 subjects showed no change, and 2 showed decreases of –0·01.

PULSE TRANSMISSION TIME
The decrease in pulse transmission time from standing to 2 minutes of squatting was significant (mean decrease –4·3; $P < 0{\cdot}001$) but the other two comparisons were not (standing vs. onset of squatting –1·5 ms; $P > 0{\cdot}2$ and onset of squatting vs. 2 minutes of squatting –2·8 ms; $P > 0{\cdot}1$).

Discussion

Our subjects' decreases in heart rate represent the expected bradycardia which occurs with squatting (O'Donnell and McIlroy, 1962; Nellen *et al.*, 1967, 1968; Fontana *et al.*, 1975). The large increases in ejection time were clearly disproportionate to the decreases in rate (Figure), as further documented by the increase in ejection time index, i.e. when heart rate effects on LVET were accounted for, the resultant index still shows a large increase over standing control with prompt squat and this was sustained over 2 minutes of squatting. Thus, the increases in ejection time are not solely the result of the squatting bradycardia, in which case the ejection time index would be stable (Weissler *et al.*, 1969), but appear also to reflect the known increases in stroke volume with squatting (O'Donnell and McIlroy, 1962; Nellen *et al.*, 1967).

The pre-ejection period is comprised of q-I_m and the isovolumic contraction time. Changes in q-I_m are small compared with those in isovolumic contraction time and the similarity in results of the contraction time and the pre-ejection period clearly suggest the dominant influence of the duration of isovolumic contraction time on the pre-ejection period during squatting. The pronounced reductions in these 2 intervals, with the increases in ejection time index are typical of stroke volume increases (Lewis *et al.*, 1974) and indicate a Starling effect via increased venous return. During sustained squatting reductions in the isovolumic contraction and pre-ejection periods from standing control levels were not as great as those seen at the onset. Changes in venous return, contractility, and afterload could all influence this change but invasive procedures would be required for further documentation.

There was a mean decrease in pulse transmission time at the onset of squatting. While chronic shortening of pulse transmission time in conditions such as atherosclerosis is well known and understood, reasons for changes in pulse transmission time during acute interventions remain more obscure. Among the many challenges investigated in our laboratory, the pulse transmission time has nearly always remained stable despite large changes in heart rate and systolic time intervals (Lance and Spodick, 1975). The largest exception in our experience occurred with isometric exercise (Quarry and Spodick, 1974). Since diastolic pressure increases significantly with isometric exercise but not with many of the other challenges investigated, it was suggested in previous investigations that increases in arterial diastolic pressure might be influential in effecting the decrease in pulse transmission time (Lance and Spodick, 1975). Since diastolic pressure tends to increase with squatting (Nellen *et al.*, 1967), this same relation may again be suggested.

Finally, the overall effects of prompt versus more prolonged squatting must be considered. Nellen *et al.*, in studying the effect on the systolic murmur in hypertrophic obstructive cardiomyopathy, report that squatting had to be prompt to achieve the optimum results (Nellen *et al.*, 1967, 1968). While our results for heart rate and pulse transmission time indicate that not all maximal values are achieved at the onset of squatting, the greatest changes do occur promptly.

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Left ventricular endomyocardial fibrosis in India

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Clinical, radiological, electrocardiographic, haemodynamic, and cineangiographic features of left ventricular endomyocardial fibrosis are described in 8 patients seen during the 10-year period 1965-1975. Exertional dyspnoea was the commonest presenting symptom. Mild to moderate cardiomegaly was often present. The apex beat was never forcible. A loud third heart sound over the apex and an apical early systolic murmur with late systolic decrescendo were characteristic of this disease. Chest x-*ray films showed left atrial enlargement and pulmonary venous congestion. A pronounced rise in left ventricular end-diastolic pressure, severe pulmonary hypertension, and low cardiac index were seen in 6. Ventriculography showed an irregular, poorly contracting left ventricle with areas of dyskinesis and large end-systolic volume. Mitral regurgitation, when present, was not severe.*

In 1953, following a suggestion from Dr. J. D. Ball, a former staff member of this Institution, a search was made in our necropsy material for endomyocardial fibrosis. Material from 3 cases was later sent to Professor Davies in Uganda, who confirmed the diagnosis. After the publication of this work by Samuel and Anklesaria (1960) necropsy reports of endomyocardial fibrosis were published from various parts of India (Shah *et al.*, 1962; Mehrothra *et al.*, 1964; Kinare and Deshpande, 1965; Reddy *et al.*, 1965; Reddy *et al.*, 1969; Reddy *et al.*, 1970). They described involvement of both ventricles or the left ventricle alone. During a 10-year period (1965 to 1975) we have seen 25 cases of endomyocardial fibrosis. Necropsy data were available from 11 patients and in all of them the left ventricle was involved. There is therefore good evidence of frequent gross anatomical changes involving the left ventricle in patients in India suffering from endomyocardial fibrosis but there has not been any report from this country of the clinical features of left ventricular endomyocardial fibrosis.

Subjects and methods

During the 10 years from 1965 to 1975 5100 patients were studied in the cardiac catheterisation laboratory of this hospital, of whom 12 were found to have endomyocardial fibrosis. In 8 of them the left ventricle was involved, 3 having isolated left ventricular involvement and 5 biventricular endomyocardial fibrosis, and their clinical features are described here. Their ages varied from 7 to 31 years; 6 were male and 2 were female patients. Six of them were students, one a farmer and another an ex-service man. Only 3 of them belonged to the poor socioeconomic group of this country.

The diagnosis of endomyocardial fibrosis was suspected on clinical grounds and confirmed in all by cardiac catheterisation and selective cineangiocardiography. Chest *x*-rays in the posteroanterior view and with barium swallow in the right anterior oblique view were available in all cases. They were carefully examined fluoroscopically to detect intracardiac calcification. Standard 12-lead electrocardiograms were also obtained. Cardiac catheterisation was performed under light sedation with phenobarbitone and promethazine hydrochloride. Pressure data were recorded by means of a Statham P23Db pressure transducer connected to an Electronics for Medicine 8-channel photographic recorder. Cardiac output was calculated by the Fick principle. Left ventriculography was done in the right anterior oblique view using 1 ml per kg of 76 per cent Urografin injected under pressure and filming at 36 frames per second.

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Results and analysis

SYMPTOMS

Seven patients had progressive exertional dyspnoea, of whom 2 were in severe congestive heart failure. One patient had paroxysmal nocturnal dyspnoea and haemoptysis. A history of vague joint pains at the onset of the disease was reported in 2 subjects. Right hemiplegia was present in a 16-year-old girl (case 4). The youngest of our patients, a 7-year-old boy, was brought by his mother (a nurse) who noticed unusual neck vein pulsations. He was completely asymptomatic.

PHYSICAL SIGNS

The triad of raised jugular venous pressure, hepatomegaly, and ascites characteristic of right ventricular endomyocardial fibrosis was present in 3 patients. The other 2 patients with biventricular involvement had only a raised jugular venous pressure as evidence of right ventricular involvement. All patients were in sinus rhythm. Case 7, a 31-year-old ex-service man with biventricular involvement, while in hospital, developed atrial fibrillation resulting in pronounced deterioration. The apex beat was well felt in all these patients, but was never forcible. Moderate cardiomegaly was present in 7 patients. Case 5 had a normal sized heart. A moderate left parasternal heave was felt in 5 patients while in 2 others a mild one was present. A palpable second heart sound was felt in the second left sternal border in 5 patients, but none of them had visible or palpable pulsations in that area. The first heart sound was loud in 4 patients. An accentuated pulmonary second sound was present in 6 subjects. A loud third heart sound was audible over the apex in all the 8 patients, while 3 of them had an additional fourth heart sound. All the 5 patients with biventricular involvement had a loud right ventricular third heart sound over the tricuspid area and epigastrium, with a pansystolic murmur of tricuspid regurgitation in 2 of them. An apical early systolic murmur with late systolic decrescendo was heard in 6 of our patients. Crepitations over lung bases were heard in 4 patients.

RADIOLOGICAL SIGNS

Plain *x*-ray films of the chest closely resembled those of patients with rheumatic mitral stenosis (Fig. 1). There was mild to moderate left atrial enlargement and dilated prominent superior pulmonary veins in all the patients. Pronounced hilar clouding and septal lines were noticed in 3 of them. Even though significant pulmonary hypertension was detected during catheterisation in 6 patients, none showed the expected degree of dilatation of the main pulmonary artery or its primary divisions. Only 1 of the 5 patients with biventricular involvement had a large right atrium. Others had only mild to moderate right atrial enlargement even though the right atrial pressure was very high. Diagnostic ventricular calcification was present in 3 patients and was extensive, involving both ventricles, in 2 of them (Fig. 2).

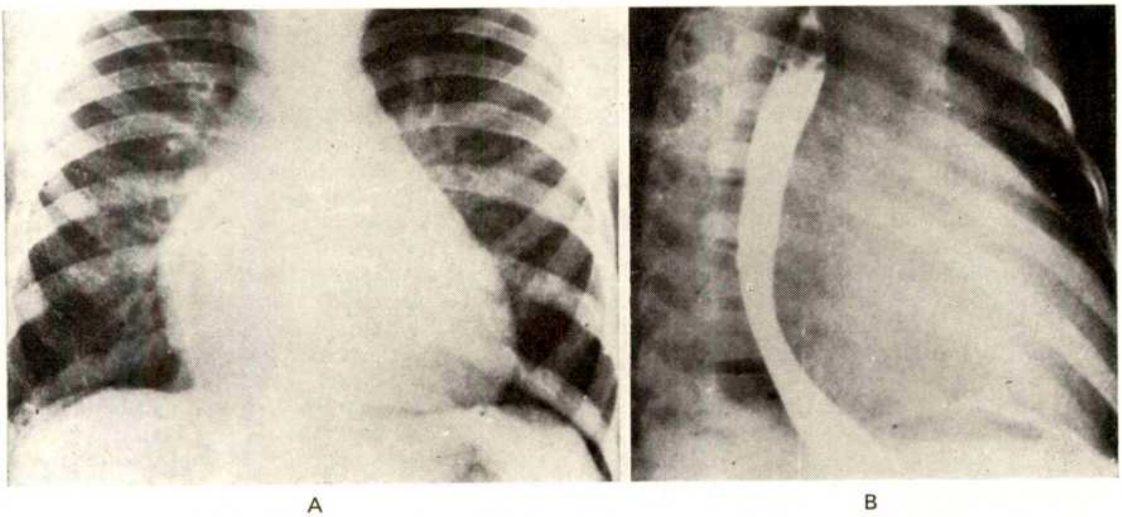
A B

Fig. 1 X-*ray film of chest (case 2). (A) Posteroanterior view showing perihilar venous congestion. The main pulmonary artery is not prominent despite the pulmonary artery pressure of 62/32 mmHg. (B) Right anterior oblique view with barium showing moderate left atrial enlargement.*

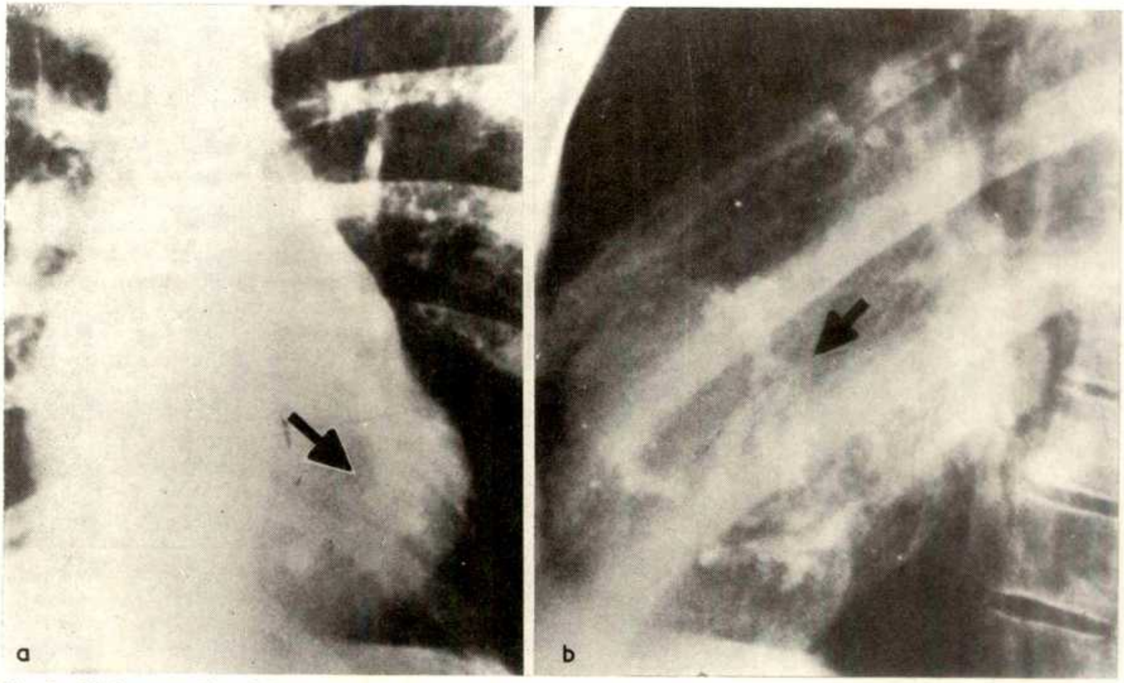

Fig. 2 *Plain* x-*ray film of the chest (case 7). (a) Posteroanterior and (b) lateral views showing extensive intracardiac calcification. Note also enlarged left atrial appendage in posteroanterior view.*

ELECTROCARDIOGRAPHIC SIGNS

All patients showed left atrial P waves and one had evidence of right atrial enlargement in addition. Two had left axis deviation and both had extensive left ventricular calcification. Only 2 patients had evidence of left ventricular hypertrophy.

CARDIAC CATHETERISATION FINDINGS

Table 1 summarises the right and left heart catheterisation data. All the 5 patients with biventricular endomyocardial fibrosis showed a raised right atrial pressure and right ventricular end-diastolic pressure characteristic of right ventricular involvement.

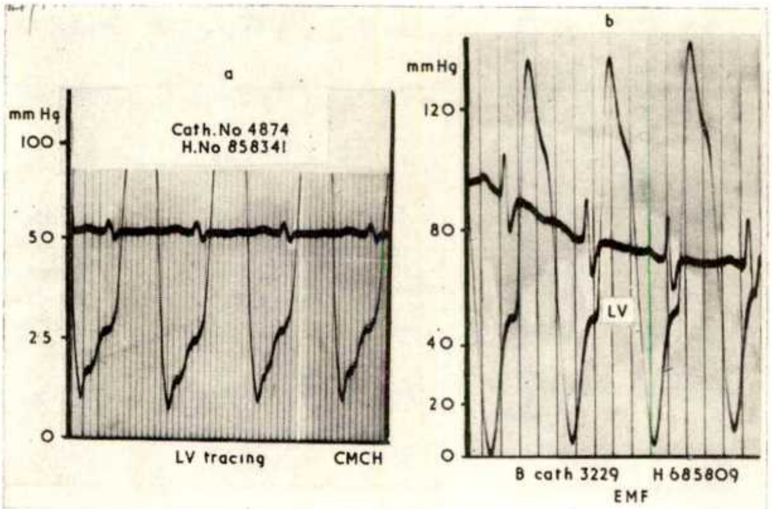

Fig. 3 *(a) Left ventricular pressure tracing showing raised early diastolic pressure and gradual rise of pressure till end diastole. Note that the pressure does not come to a 'plateau' in mid or late diastole. (b) Left ventricular pressure tracing. End diastolic pressure (45 mmHg) is more than one-third the peak systolic pressure.*

Mean right atrial pressure was normal in patients with isolated left ventricular involvement. With the exception of Case 5, all others had pulmonary hypertension with pronounced rise in the pulmonary wedge pressure. Left ventricular end-diastolic pressure was raised in all of them and none had any diastolic gradient across the mitral valve. Left ventricular dip or early diastolic pressure was also raised in all of them. The left ventricular pressure tracing did not show the diastolic dip and plateau pattern. From the early diastolic dip the pressure continued to rise till end-diastole without forming a plateau (Fig. 3a). It was not uncommon for the left ventricular pressure to reach as high a level as one-quarter to one-third of the peak systolic pressure (Fig. 3b). The cardiac index was low in 6 patients. There was a conspicuous rise in the pulmonary vascular resistance.

CINEANGIOGRAPHIC SIGNS

Diagnosis of endomyocardial fibrosis was confirmed by ventriculography and the findings are given in Table 2. The shape of the left ventricle was irregular in all cases. Multiple small aneurysmal areas were present around the apex of the left ventricle in 3 patients. In others the apex appeared rounded and showed hypokinesia. Three patients showed generalised hypokinesia in addition. The left ventricular cavity was small in 2, normal in 5, and enlarged in 1 patient. Because of the hypokinesia and/or aneurysms over the apex, the end-systolic volume was increased and the ejection fraction small.

Table 1 *Cardiac catheterisation data*

Case No.	*Ventricle involved*	*Pressures (mmHg)*						*CI (l/m per m²)*	*PVR (units)*
		RA *a/v* *x/y*	*RV*	*PA*	*mPW*	*Ao*	*LV*		
1	LV	5/2–5 4/1	54/0–2	64/30	28	92/62	92/8–25	2·3	7·6
2	LV	10/7 3/7	60/4–8	63/32	18	90/66	96/4–16	2·0	11·0
3	LV	8/5 3/4	72/0–6	72/44	24	96/66	96/10–24	1·7	21·0
4	LV+RV	15/10 5/9	44/2–10	52/30	27	80/55	94/7–20	1·7	7·6
5	LV+RV	12/8 4/4	20/0–12	16/12	12	104/75	108/0–13	3·1	0·3
6	LV+RV	30/30 25/27	64/3–25	60/36	36	100/80	100/0–45	2·3	5·1
7	LV+RV	14/15 11/12	68/6–14	62/14	36	80/60	80/14–25	2·3	2·6
8	LV+RV	10/7 6/4	95/4–10	80/40	27	110/75	110/6–25	4·0	9·7

RA, right atrium; RV, right ventricle; PA, pulmonary artery; mPW, mean pulmonary wedge; Ao, aorta; LV, left ventricle; CI, cardiac index; PVR, pulmonary vascular resistance.

Table 2 *Left ventriculographic signs*

Case No.	*Size*	*Shape*	*Contractility*	*End-systolic volume*	*Areas of dyskinesis*	*MR*	*Thrombus filling defect*
1	Enlarged	Irregular	Poor	Large	Present	Trivial	No
2	Normal	Irregular	Poor	Large	Present	Mild	No
3	Small	Irregular	Poor	Large	Present	Mild	No
4	Normal	Irregular	Poor	Large	Present	Mild	No
5	Normal	Irregular	Fair	Large	Present	Trivial	No
6	Normal	Irregular	Poor	Large	Present	Moderate	Large
7	Normal	Irregular	Very poor	Large	Present	Mild	No
8	Small	Irregular	Poor	Large	Present	Moderate	No

MR, mitral regurgitation.

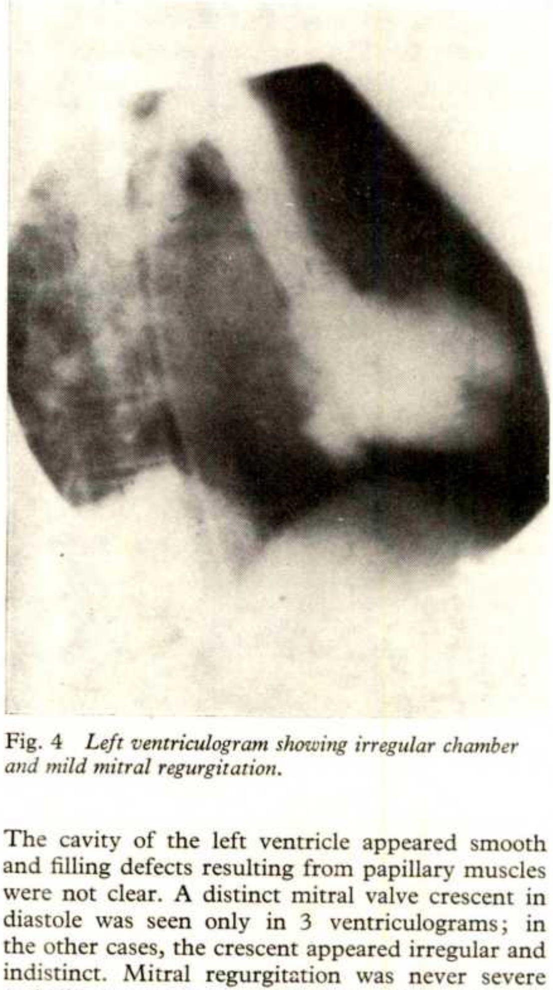

Fig. 4 *Left ventriculogram showing irregular chamber and mild mitral regurgitation.*

The cavity of the left ventricle appeared smooth and filling defects resulting from papillary muscles were not clear. A distinct mitral valve crescent in diastole was seen only in 3 ventriculograms; in the other cases, the crescent appeared irregular and indistinct. Mitral regurgitation was never severe and did not produce systolic expansion of the left atrium. Case 6 showed multiple irregular thrombi. The aorta was small and the coronary arteries appeared normal. A pericardial effusion was not present in any of these patients.

Discussion

Right ventricular endomyocardial fibrosis presents with distinctive clinical findings (Ball *et al.*, 1954; Abrahams, 1962; Somers *et al.*, 1968). But left ventricular endomyocardial fibrosis has few distinctive signs by which it can be differentiated from rheumatic heart disease and left ventriculography is essential for the diagnosis. A clinical syndrome as described by Fowler and Somers (1968) is characterised by an early mitral systolic murmur, a third heart sound, and often an opening snap ascribed to a mobile anterior cusp. Fibrosis often affects the apex of the left ventricle and the posterior wall (Davies and Ball, 1955; Connor *et al.*, 1967, 1968). The posterior cusp of the mitral valve may become adherent to the fibrotic scar in the posterior left ventricular wall. The anterior cusp usually shows no evidence of thickening, shrinkage, or scarring; its papillary muscle is normal even though it is inserted into the apical scar. Because of these unique pathological features, mitral regurgitation occurs only in the first half of systole as the normal anterior cusp maintains competence in late systole. The opening snap produced by this normal anterior cusp was present in 6 of the 12 patients in the series reported by Fowler and Somers (1968), but we did not find this clinical sign in any of our patients. Moreover, 2 of our patients had a pansystolic murmur with late systolic decrescendo and they had moderate mitral regurgitation on left ventriculography. These features may well have been the result of a more advanced stage of left ventricular fibrosis in our patients.

Right ventricular endomyocardial fibrosis is often associated with aneurysmal dilatation of the right atrium caused by the conspicuously raised right atrial pressure. Even though the left atrial pressure was raised to very high levels, only mild to moderate left atrial enlargement was present in our patients. Moreover, unlike isolated right ventricular endomyocardial fibrosis, right ventricular involvement in biventricular endomyocardial fibrosis seems to be associated with only mild to moderate right atrial dilatation. Intracardiac calcification when present was diffuse and did not have any characteristic distribution. Calcification was seen only in patients with a severe form of the disease. Since Cockshott *et al.* (1967) described this abnormality, reports of such gross calcification involving both ventricles have rarely been published.

One other feature in 6 of our patients was a disparity between the clinical, electrocardiographic, and radiological signs, and the degree of pulmonary hypertension. Five patients had severe pulmonary hypertension as shown by a pulmonary vascular resistance greater than 7·5 units. This was not obvious clinically nor did the electrocardiogram show right axis deviation or right ventricular hypertrophy. The chest *x*-ray showed only slight prominence of the main pulmonary artery segment in 2 of them. Inconspicuous dilatation of the pulmonary artery may be an indication of involvement of the right ventricle by the same pathological process or the effect of a persistently low cardiac output. Pulmonary hypertension was always accompanied by a very high left ventricular end-diastolic pressure. A raised left ventricular end-diastolic pressure had no relation to the degree of mitral regurgitation. Four of our patients with trivial to mild mitral regurgitation had severe pulmonary hypertension. It appears that the restriction of ventricular filling by endocardial fibrosis and the consequent rise in left ventricular diastolic pressure lead to the development of pulmonary hypertension.

From the foregoing discussion it is evident that the absence of a prominent apical impulse, the presence of a loud third heart sound over the apex, an apical early systolic murmur with late systolic decrescendo, and moderate left atrial enlargement with pronounced pulmonary venous congestion on the *x*-ray film, are characteristic of left ventricular endomyocardial fibrosis. Unlike rheumatic mitral regurgitation, the clinical symptoms and pulmonary venous congestion are out of proportion to the amount of mitral regurgitation. Even though some of these physical signs may help in differentiating left-sided endomyocardial fibrosis from rheumatic mitral regurgitation, this cannot be done with certainty without left ventriculography.

In this series we have found some patients with near normal cardiovascular findings and others with pronounced cardiomegaly and severe congestive heart failure, representing two ends of the spectrum of endomyocardial fibrosis. It appears that early involvement of the left ventricle with scattered areas of fibrosis in the apical and submitral region can be detected only by cineventriculography. This stage of the disease is followed by progressively increasing endocardial fibrosis and restriction to ventricular filling with rising ventricular end-diastolic pressure and consequent pulmonary hypertension. The involvement of the posterior mitral valve cusps, papillary muscles, and altered contraction sequence produces mitral regurgitation. These changes on the left side are often accompanied by involvement of the right ventricle. The final picture is one of severe congestive heart failure with little response to conventional forms of treatment.

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Symmetrical peripheral gangrene

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Two cases of symmetrical peripheral gangrene associated with intracardiac lesions are described. One had a secondary deposit from a uterine leiomyosarcoma in the wall of the right ventricle, the other had a free ball thrombus in the right atrium; there were no valvular lesions in either case. The published reports of this type of gangrene indicate that it may result from (1) vasospastic conditions, (2) small vessel obstruction, or (3) conditions producing a very low cardiac output. The two patients reported are unusual examples of the last.

Symmetrical peripheral gangrene is said to be present when the distal parts of two or more extremities undergo ischaemic change without obstruction to the main arteries supplying them (Goodwin and Berne, 1974). The association of this rare condition with an obstructive intracardiac lesion was first described by Von Ziemssen in 1890. This led in subsequent years to case reports of symmetrical peripheral gangrene in which the presence of a left atrial ball thrombus caused by mitral stenosis was suspected clinically and confirmed at necropsy (Bozzolo, 1896; Battistini, 1909; Lutembacher, 1917; Aubertin and Rime, 1926; Covey *et al.*, 1928). In 1931 Schwartz and Biloon described 3 cases of symmetrical peripheral gangrene. Two had left atrial ball thrombi secondary to mitral stenosis and the third had hypertensive heart failure and a left atrial thrombus but without valvular disease.

Symmetrical peripheral gangrene has been described in other conditions in which there is a fall in cardiac output. It has been noted after myocardial infarction (Swan and Henderson, 1951; Cotton and Bedford, 1956; Cohen, 1961), in hypertensive heart failure (Perry and Davie, 1939) and with resistant ventricular tachycardia (Abrahams, 1948).

We present 2 cases of peripheral gangrene associated with intracardiac lesions. In one there was a secondary leiomyosarcoma in the right ventricular wall, and in the other a large ball thrombus of the right atrium. These cases are unusual in that the right side of the heart was affected, and also in that no valvular lesion was found at necropsy.

Case reports

CASE 1

A 53-year-old woman was admitted with cyanosis of her feet and hands. She had had a uterine leiomyosarcoma removed one year previously. On examination she had incipient gangrene of the cheeks, nose, feet, and hands, and demarcation developed as shown (Fig. 1 and 2). She had a sinus tachycardia of 100/min and blood pressure of 135/105 mmHg. The heart was enlarged. Her jugular venous pressure was raised but her peripheral veins were collapsed so that venepuncture was difficult. Both radial pulses were palpable, but no pulses were felt below the femorals. There was a diastolic murmur at the left sternal border and a loud systolic murmur in the pulmonary area. She died one month after admission.

At necropsy a secondary deposit of leiomyo-

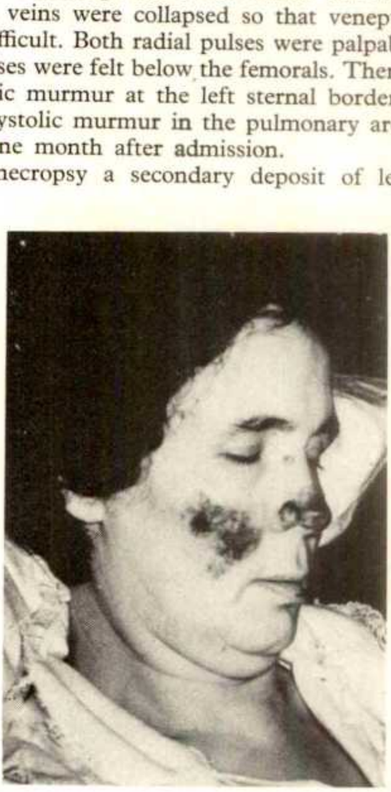

Fig. 1 *Ischaemic involvement of nose and cheeks in case 1.*

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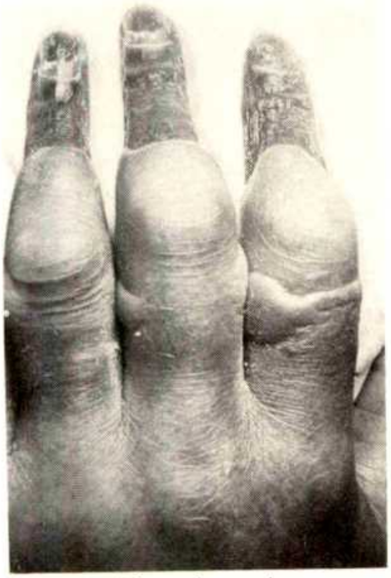

Fig. 2 *Gangrene of fingers in case 1.*

sarcoma was found in the anterior wall of the right ventricle almost obliterating the cavity. Two secondary deposits were present in the lungs. There was no evidence of local recurrence. No evidence of arterial thrombosis or embolus was found in the femoral, popliteal, dorsalis pedis, or ulnar vessels on macroscopical or histological examination. Recent antemortem thrombus was found in the portal vein but no antemortem thrombi or emboli were found elsewhere in the venous system. The coronary arteries were normal.

CASE 2

A 71-year-old woman was admitted complaining of breathlessness and weakness. She had noticed 2 days before that her nose and cheeks had become blue. There was a past history only of bronchitis. For the previous 2 months she had become increasingly dyspnoeic and had lost weight. On examination she had intense cyanosis of her nose and cheeks. Her left hand was cold and the nail beds of the second, third, fourth, and fifth fingers were cyanosed. Both feet were cold and slightly cyanosed. There was a concentric area of ischaemia and ulceration around her perineum (Fig. 3). She had a deep venous thrombosis of her right leg. Her blood pressure was 120/80 mmHg. Her pulse was 80 and fibrillating. Her jugular venous pressure was not raised. Both radial pulses were palpable though the left was weaker. No pulses were felt in her legs. On admission haemoglobin 13·6 g/dl, platelets 54×10^9/l, white blood count $17{\cdot}2 \times 10^9$/l, 85 per cent polymorphs. Fibrinogen degradation products greater than 80 and less than 160. Treatment was started with intravenous heparin, but she continued to deteriorate and gangrene of her fingers developed (Fig. 4). She died 48 hours after admission.

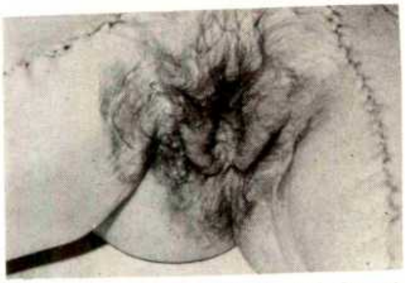

Fig. 3 *Concentric area of ischaemia and ulceration around the perineum in case 2.*

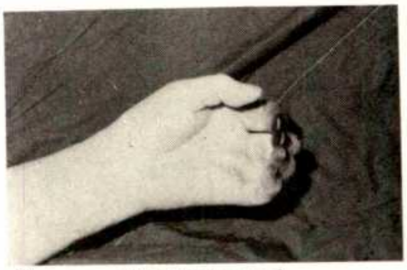

Fig. 4 *Gangrene of fingers in case 2.*

At necropsy there was moderate atheroma of the aorta. A thin plaque of antemortem thrombus was adherent to the posterior wall of the abdominal aorta and there was a similar thrombus in the left common iliac. There was a deep venous thrombosis of the right femoral vein extending to the right common iliac vein. Both pulmonary arteries were almost obliterated by adherent antemortem thrombus of some days' duration. There was a large free ball thrombus, 43 mm × 37 mm in the right atrial appendix and numerous small warty thrombi were adherent to the right atrial and ventricular walls (Fig. 5). One similar adherent thrombus was found in the left atrial appendix. There was no valvular disease. Carcinoma was not found.

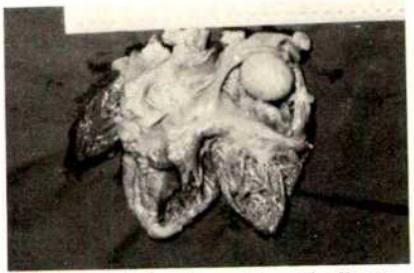

Fig. 5 *Right atrial thrombus and small adherent thrombi in case 2.*

Discussion

In addition to the peripheral limb ischaemia found in symmetrical peripheral gangrene, the nose, cheeks, ear lobes, and occasionally the perineum may also be involved. The causes of this syndrome fall into three main groups: (1) vasospastic conditions such as Raynaud's syndrome (Raynaud, 1888), ergot poisoning (Cranley *et al.*, 1963), and frostbite (Dunning, 1964); (2) conditions in which the small vessels are obstructed, such as disseminated intravascular coagulation (Goodwin and Berne, 1974), the presence of cold agglutinins, or primary thrombocythaemia (Preston *et al.*, 1974) and Lloyd *et al.* (1967) described 4 cases in children in which the presumptive diagnosis was polyarteritis nodosa; it has also been described in children after infectious diseases such as chickenpox (Gyde and Beales, 1970) and measles (Chaudhuri and McKenzie, 1970) where intravascular coagulation was probably responsible; and (3) conditions leading to a fall in cardiac output—our cases belong to this third group.

Peripheral gangrene of the limbs alone is rarely a consequence of extensive venous obstruction caused by thrombosis and occasionally more than one limb may be involved (Ross *et al.*, 1961).

The possibility of diagnosing clinically an occluding atrial thrombus was first suggested by Von Ziemssen in 1890, when he described circumscribed gangrene of the feet with absent or diminished arterial pulsation in the legs in 3 patients found to have large left atrial thrombi and mitral stenosis. The association of symmetrical peripheral gangrene with myocardial infarction, hypertensive heart disease, and arrhythmia has since made it clear that the fall in cardiac output responsible may simply be a result of failure of the heart as a pump, without actual obstruction to flow.

In 1938 Fishberg suggested that the cause of the gangrene was intense peripheral vasoconstriction in an attempt to maintain the blood pressure and circulation to vital organs in the presence of a grossly reduced cardiac output. In his patients he found that, while the neck veins were engorged, the peripheral veins were collapsed and venepuncture was difficult, suggesting poor peripheral flow. He drew attention to the fact that in severe right heart failure the cervical veins were often more engorged than the peripheral veins, presumably a lesser manifestation of this. Fishberg also mentions (1944) that he has seen symmetrical peripheral gangrene in tight mitral stenosis without ball-valve impaction.

Necropsy of the peripheral blood vessels of these patients has consistently failed to reveal thrombosis or emboli, and it has been shown by Roddie and Shepherd (1957) that the blood flow through human digital arteries falls to zero when the perfusion pressure may still be 36 to 60 mmHg.

Intense cyanosis of the nail beds and cold peripheries is occasionally seen in patients with severe myocardial infarction, but such a dramatic fall in cardiac output is associated with a high mortality, and these patients usually die before frank peripheral gangrene can develop. In our first case the coronary arteries were normal and peripheral vasoconstriction enabled her to maintain an adequate blood flow to her vital organs as the obstruction in her right ventricle increased.

In case 2 the thrombus present in both pulmonary arteries was at least as responsible for the fall in cardiac output as the ball thrombus in the right atrium, and the condition has been described after pulmonary embolus alone (Hejtmancik and Bruce, 1953). There was haematological evidence of intravascular coagulation, and multiple thrombi were found at necropsy, but the distribution of the peripheral ischaemia, particularly of the perineum, suggests that this was the result of vasoconstriction rather than intravascular coagulation. It is in keeping with Fishberg's proposed aetiology that both our patients maintained a reasonable blood pressure while the peripheral gangrene progressed.

We thank Dr. J. N. Mickerson for permission to report on a case under his care and for his helpful criticism.

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Pulmonary atresia with intact ventricular septum
Open heart surgical correction at 32 hours

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A case of pulmonary atresia with intact ventricular septum is reported in which total surgical correction was carried out successfully at 32 hours of age. Cardiac catheterisation at 17 months has revealed virtually normal haemodynamic and angiographic findings. Surgical correction of this condition in the neonatal period is discussed.

When the pulmonary valve is atretic and the ventricular septum is intact, systemic venous return enters the left atrium via a patent foramen ovale or atrial septal defect. The lungs are perfused by aortopulmonary collateral vessels or a persistent ductus arteriosus, and hypoxia is frequently severe. Patients present in the early neonatal period with severe right heart failure and cyanosis. There may be a systolic murmur of tricuspid regurgitation or continuous murmur of a persistent ductus arteriosus and the second heart sound is single.

The chest radiograph shows oligaemic lung fields and cardiac enlargement with a prominent right atrium. The electrocardiogram shows an inferiorly directed mean frontal QRS axis, tall P waves in lead II, and either a low R/S ratio in lead V1 or right ventricular hypertrophy. The echocardiogram is not very helpful but the pulmonary valve is not seen. Cardiac catheterisation and angiocardiography are diagnostic.

In most cases the main pulmonary artery is patent and therefore total correction or palliative surgery can usually be attempted.

Case report

The patient was a full-term normal infant weighing 4·05 kg and was centrally cyanosed at birth. At 24 hours there was severe cyanosis with right heart failure, a pansystolic murmur at the left sternal edge, and single second heart sound. The electrocardiogram showed tall P waves in lead II, and R/S ratio of 0·8 in lead V1, and a mean frontal QRS axis of +90°. The chest radiograph (Fig. 1a) showed oligaemic lung fields and cardiac enlargement with a prominent right atrium. At right heart catheterisation with selective right (Fig. 2a) and left ventriculography, the appearances were those of pulmonary atresia with intact ventricular septum, patent foramen ovale, and persistent ductus arteriosus. The right ventricle was hypoplastic with pronounced infundibular narrowing and there were multiple sinusoids communicating with the coronary veins. The main pulmonary trunk, filling via the persistent ductus arteriosus, was of good size and extended proximally to an atretic pulmonary valve. Balloon atrial septostomy was performed.

At operation (L.D.A.) at 32 hours of age, the patient was surface cooled to 25°C with 'Cryogel' packs and then to 18·5°C using extracorporeal circulation. Deep hypothermia with circulatory arrest was maintained for 26 minutes. The persistent ductus ateriosus was ligated. The main pulmonary artery was opened revealing an imperforate pulmonary valve with three normal-sized cusps. The fused commissures were incised. Infundibular muscle was resected through a transverse right ventriculotomy and the atrial septal defect was closed through a right atriotomy. The patient developed severe right heart failure in the immediate postoperative period, but this gradually responded to diuretics, though treatment with frusemide was required until the age of 5 months.

At 17 months she was thriving and was developing normally. There was then a short systolic ejection murmur at the left sternal edge, a normally split second heart sound, and an early diastolic murmur in the second left intercostal space. The

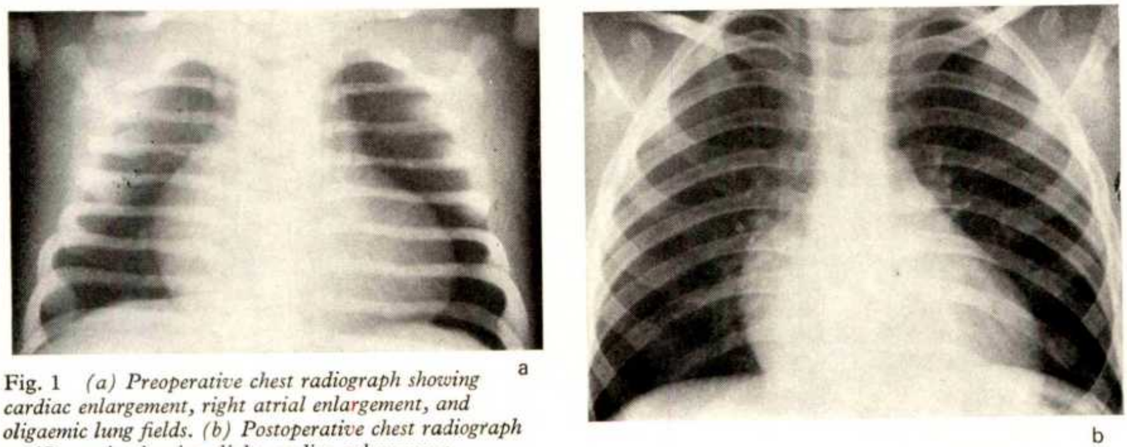

Fig. 1 *(a) Preoperative chest radiograph showing cardiac enlargement, right atrial enlargement, and oligaemic lung fields. (b) Postoperative chest radiograph at 17 months showing slight cardiac enlargement.*

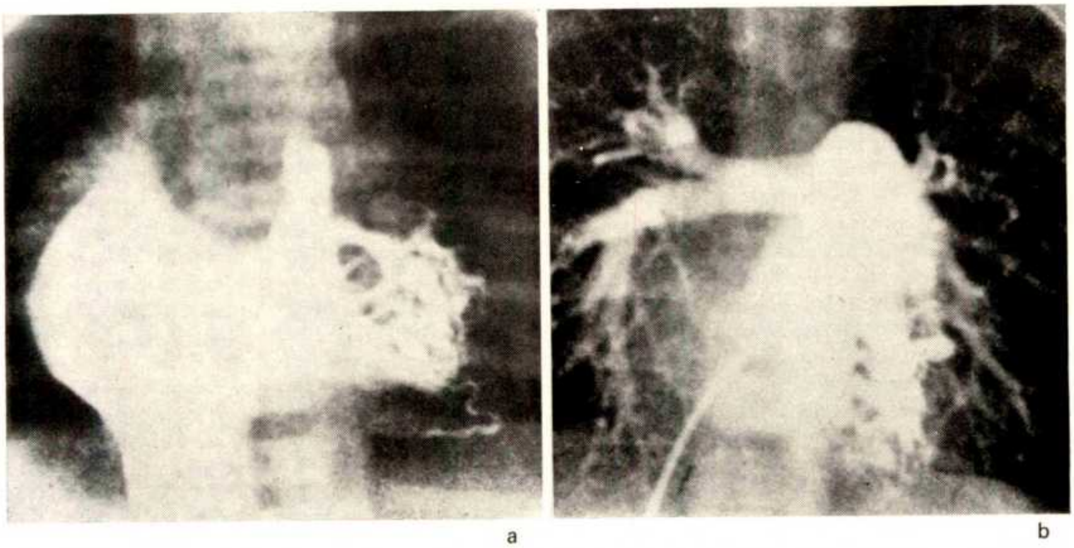

Fig. 2 *(a) Preoperative right ventriculogram showing severe tricuspid regurgitation, multiple intramyocardial sinusoids, and a blind outflow tract. (b) Postoperative right ventriculogram showing normal-sized right ventricle and pulmonary arteries, with trivial tricuspid regurgitation.*

chest *x*-ray (Fig. 1b) showed slight cardiac enlargement with a prominent right atrium and normal vascularity of the lung fields. The electrocardiogram showed a mean frontal QRS axis of +120°, but was otherwise normal. At right heart catheterisation (Table), selective right ventricular angiography (Fig. 2b) showed a large trabeculated right ventricle with a wide outflow tract leading to a normal sized pulmonary artery, and a trace of regurgitation through a normally situated tricuspid valve. There was no evidence of a residual atrial septal defect on angiography or oximetry and the catheter would not pass from the right to the left atrium.

Discussion

Pulmonary atresia with intact ventricular septum has been classified into 2 groups, according to the size of the right ventricular cavity (Greenwold *et al.*, 1956; Davignon *et al.*, 1961). It has been thought that type II (large right ventricle) was more amenable to correction by pulmonary valvotomy and carried a better prognosis than type I (hypoplastic right ventricle). It seems that there is a spectrum of severity in those patients with hypoplasia of the right ventricle (Gersony *et al.*, 1967; Bowman *et al.*, 1971; Miller *et al.*, 1973) bit intramyocardial

Table *Postoperative pressures (at 17 months)*

Right atrium (mmHg)	*Right ventricle (body) (mmHg)*	*Right ventricle (outflow) (mmHg)*	*Pulmonary artery (mmHg)*	*Pulmonary artery wedge (mmHg)*	*Femoral artery (mmHg)*
a=9, x=6 v=9, y=6 (mean 7)	26/5 (end diastolic 10)	26/5 (end diastolic 10)	19/8 (mean 11)	(mean 10)	84/50 (mean 66)

sinusoids can almost always be demonstrated (Lauer *et al.*, 1964). Our patient had a hypoplastic right ventricle with intramyocardial sinusoids (type I). It is significant that after operation the right ventricle grew to a normal size and the tricuspid regurgitation became trivial. We are not aware of any other reports of total correction at such an early age.

The place of pulmonary valvotomy for neonates with pulmonary atresia, intact ventricular septum, and varying degrees of hypoplasia of the right ventricle is debatable (Greenwold *et al.*, 1956; Vlad, 1973). There have been reports of survival after pulmonary valvotomy in patients with hypoplastic as well as in those with large right ventricles (Gersony *et al.*, 1967; Celemajer *et al.*, 1968; Cole *et al.*, 1968; Dhanavaravibul *et al.*, 1970; Bowman *et al.*, 1971; Murphy *et al.*, 1971; Shams *et al.*, 1971), but it has been suggested (Miller *et al.*, 1973) that some of these reports may have included patients with critical pulmonary stenosis, the prognosis of which is much better. Shams and co-workers (1971) reported 7 survivors of 8 patients in whom aortopulmonary shunts were performed and atrial septal defects created. Rook and Gootman (1971) reported 3 cases of type II pulmonary atresia who survived pulmonary valvotomy, though 2 patients required an additional shunt operation.

The conventional approach to operation for pulmonary atresia with intact ventricular septum is probably that advocated by Vlad (1973). He recommends balloon atrial septostomy (Miller *et al.*, 1969) and aortopulmonary shunt for all patients with a hypoplastic right ventricle, but pulmonary valvotomy when the ventricle is large. With this approach he reports a 44 per cent survival. It is clear, however, that some patients with type I pulmonary atresia do well after valvotomy and that the right ventricle may grow normally, and that pulmonary valvotomy will not always be successful in patients with a large right ventricle (type II). Our patient underwent open pulmonary valvotomy with outflow tract resection, and this more extensive procedure may have resulted in greater haemodynamic improvement, allowing the right ventricle to grow after operation.

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Prolapsing right atrial myxoma
Clinical and haemodynamic considerations

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A 22-year-old woman with a right atrial myxoma prolapsing to the right ventricle is described. The haemodynamic findings were similar to those of cases of prolapsing myxoma of the left atrium; a notching on the ascending limb of the right ventricular pressure curve, and an initial negative, irregular deflection on the pulmonary artery pressure curve with a pronounced rise in the mean right atrial pressure (18 mmHg) were found. On deep inspiration there was a significant deepening of the y *descent from 12 mmHg to 2 mmHg, indicating a changing, dynamic obstruction of the right ventricle inflow tract. These haemodynamic features can be helpful in the diagnosis of prolapsing right atrial myxoma.*

Myxomata of the atria are uncommon, especially in the right atrium (Sannerstedt *et al.*, 1962; Morrissey *et al.*, 1963). Recently, Sung *et al.* (1975) differentiated between two types of left atrial myxoma: type I, in which the tumour prolapses during diastole into the left ventricle, and type II, which is non-prolapsing. Sung described a notch in the upstroke of the left ventricular pressure curve and a rapid *y* descent in the pulmonary arterial wedge pressure curve as characteristic of the prolapsing type.

The purpose of this report is to present a case of a right atrial myxoma, prolapsing during diastole into the right ventricle, producing haemodynamic features similar to those described by Sung for the prolapsing left atrial myxoma.

Case report

A 22-year-old single woman of Arabian origin had been completely well until 6 months before her admission, when she began complaining of palpitation, frequent cough, and haemoptysis; one month before admission her complaints became worse with pain in the right posterior thorax, frequent nausea and vomiting, and a loss of 7 kg in weight. On admission she had a temperature of 37·9°C; there was no cyanosis, clubbing, or dyspnoea; her blood pressure was 120/80 mmHg, pulse rate 110/min, with regular rhythm. There was pronounced jugular venous engorgement with prominent *a* and *v* waves and a negative Kussmaul sign. Auscultation of the lungs revealed poor air entry into the right lung base and a pleural friction rub at the left base. The apex beat was palpated in the left fifth interspace in the midclavicular line; no right ventricular heave was noted. A diastolic thrill at the lower left sternal border was palpable; the first heart sound was prolonged and accentuated. The second sound was normal; a grade 4/6 mid-diastolic presystolic murmur extending into the first sound and early systole was heard at the lower left sternal border. The character of the murmur was similar to a pericardial friction rub; the intensity of the murmur was unaffected by the position of the patient but increased slightly on deep inspiration. The liver was palpable 5 cm below the costal margin and tender; the spleen was not palpable. There was mild pitting oedema in both legs.

The electrocardiogram showed sinus rhythm with a rate of 110/min, tall P waves in leads II, III, and aVF. The QRS axis was +120°, and there were no signs of right or left ventricular hypertrophy (Fig. 1a).

The sedimentation rate was 55 mm in the first hour and 85 mm in the second hour; total serum protein 84 g/l, albumin 30 g/l and globulin 54 g/l, A/G ratio 0·55 with a slight increase in β globulin and a distinct increase in γ globulin. Total bilirubin was 1·5 mg/100 ml (26·7 μmol/l), mostly indirect. Other blood chemistry was normal and haemoglobin, white cell count, platelets, and serology were within normal limits.

The chest *x*-ray film showed slight enlargement

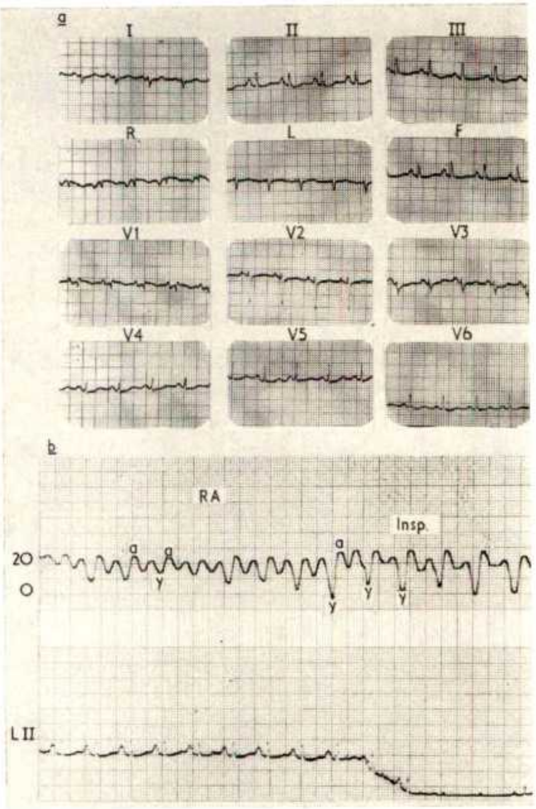

Fig. 1 *(a) An electrocardiogram showing a normal sinus rhythm, peaked P waves in leads II, III, and aVF; the QRS axis is +120°. (b) Right atrial pressure curve: the most outstanding finding is a rapid and deep* y *descent on deep inspiration.*

of the right atrium, bilateral basal pleural effusions, and the lung scan with macroaggregated albumin labelled with ^{99}Tc was suggestive of multiple pulmonary emboli.

The phonocardiogram at the lower left sternal border showed an accentuated and prolonged first heart sound and a mid to late diastolic murmur extending into the first heart sound.

HAEMODYNAMIC STUDIES

Right heart catheterisation was performed. Cardiac output was 4·0 l/min; cardiac index 2·5 l/min per m^2, stroke volume 36 ml. The various pressures recorded are listed in the Table. There was a pronounced rise in the mean pressures in the right atrium, inferior and superior vena cava (18 mmHg). There was a slight rise in the right ventricular pressure (34/8 mmHg) and a notching in the ascending limb of the right ventricular pressure. Furthermore, an early deep and irregular negative deflection of the pulmonary arterial pressure curve was noted. The most significant finding was a rapid and deep *y* descent on the right atrial pressure tracing on deep inspiration (Fig. 1b).

Table *Haemodynamic data*

Site	*Pressures (mmHg)* *Mean*		*Phasic* *a*	*x*	*v*	*y*
Superior vena cava	18					
Inferior vena cava	18					
Right atrium	18		24	15	20	14
Right atrium in inspiration	18		28	17	22	2
Right ventricle		34/8				
Pulmonary artery	24	38/20				
Pulmonary wedge	8					

Angiocardiography was performed by injecting contrast medium into the superior vena cava close to its junction with the right atrium. 70-mm films obtained in the left anterior oblique and antero-posterior position showed a large filling defect in the right atrium (Fig. 2); cineangiocardiography showed that the filling defect protruded into the right ventricle during diastole.

At operation under cardiopulmonary bypass a large tumour (8·5 × 5 × 5 cm), covered in blood

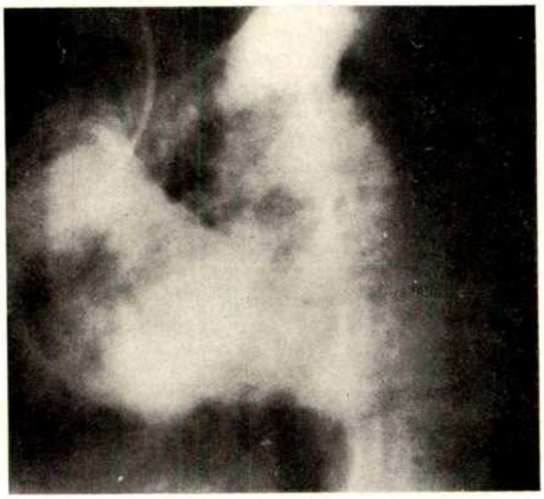

Fig. 2 *70-mm film, injection of contrast medium into the superior vena cava close to its junction with the right atrium (left anterior oblique position). A large filling defect is seen in the right atrium.*

clot, was found attached to the inferolateral wall of the right atrium, which protruded into the right ventricle: it was removed together with the adjacent area of the right atrial wall (Fig. 3). The histological examination confirmed the diagnosis of atrial myxoma. The postoperative course was uneventful, the patient recovering fully; there are now no audible murmurs and the previous jugular venous engorgement has disappeared. The tall peaked P waves in the electrocardiogram disappeared immediately after the removal of the tumour while the patient was still on the operating table. The patient gained 8 kg in true body weight within 3 months of the operation.

Discussion

The physical findings as described in our patient could erroneously lead to the diagnosis of organic tricuspid valve disease. Nevertheless, the short history, the absence of mitral valve disease, the absence of a right ventricular heave, the presence of normal sinus rhythm (Morrissey *et al.*, 1963), the high blood sedimentation rate, and hypergammaglobulinaemia, all supported the clinical diagnosis of right atrial myxoma. It is interesting that the high peaked P wave seen in the electrocardiogram in our patient and described by others in right atrial myxoma (Sannerstedt *et al.*, 1962), disappeared immediately after the removal of the tumour while the patient was still on the operating table.

Whereas in almost all reported cases of right atrial myxoma, the tumour originated from the atrial septum in the vicinity of the fossa ovalis (Nasser *et al.*, 1972 a, b), in our case it was attached to the free inferolateral wall of the right atrium. A similar location for the tumour growth has been described by Currey *et al.* (1967).

On cardiac catheterisation a notch in the upstroke of the right ventricular pressure curve was seen in our case (Fig. 2). Such a notch in the right ventricular pressure curve in right atrial myxoma has been described previously (Ramsey *et al.*, 1969) and thought to be caused by the expulsion of the protruding tumour mass during early ventricular systole across the tricuspid orifice, and back into the right atrium interfering with the early phase of ventricular contraction. A similar notch in the upstroke of the left ventricular pressure curve was also described in relation to left atrial myxoma (Pitt *et al.*, 1967). Furthermore, it was shown (Sung *et al.*, 1975) that such a notch was to be found only in those cases of left atrial myxoma

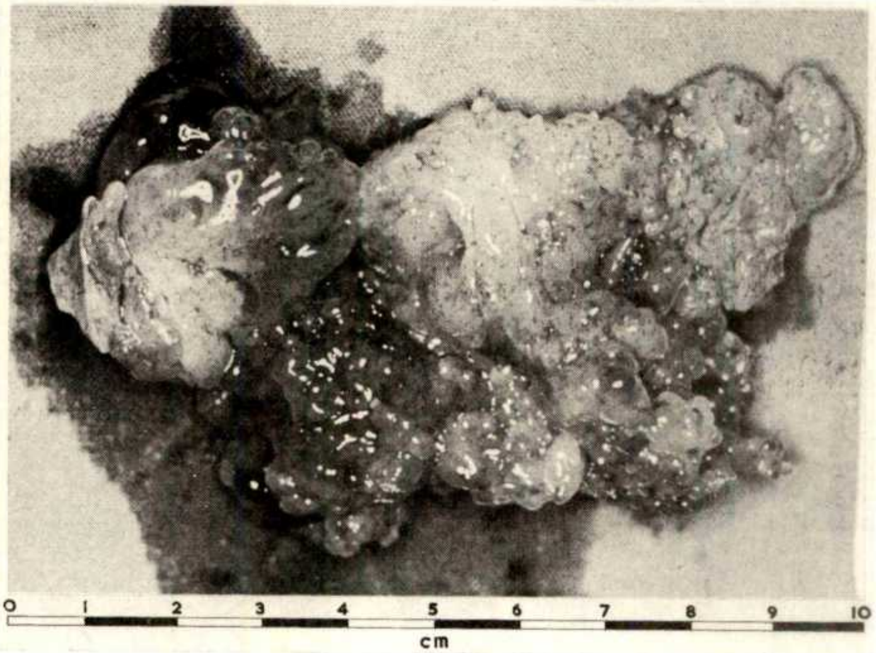

Fig. 3 *The large myxomatous tumour (8·5 × 5 × 5 cm) removed from the right atrium.*

which prolapsed during diastole into the left ventricle, and were identified as the prolapsing type. This notch, whether in the right or left ventricular pressure curves, is especially indicative of an atrial myxoma if the notch appears to vary in magnitude, degree, and position on the ascending limb, probably reflecting the changing location of the pedunculated prolapsing atrial myxoma, with each cardiac cycle. Such a notch has been considered not to be an artefact, because it was recorded only preoperatively and was absent after removal of a left atrial tumour (Nasser *et al.,* 1972 a, b).

In an experimental study in dogs (Pantazopoulos and Moscovitz, 1972), using a distensible balloon to simulate a pedunculated left atrial tumour, it was shown that moderate balloon distension caused a prominent notch on the ascending limb of the left ventricular pressure pulse, caused by displacement of the balloon from the left ventricle into the left atrium. Pronounced balloon distension caused even greater left ventricular notching, interrupted aortic blood flow during ejection, and in addition caused a rapid y descent in the left atrium pressure curve. In our case an early deep and irregular negative deflection of the pulmonary artery pressure curve was observed and could have been caused by a temporary interruption of the pulmonary arterial blood flow; though artefacts, recorded frequently in pulmonary arterial pressure curves, cannot definitely be excluded.

The finding of a slow y descent in the right atrial pressure curve suggests the presence of a static unchanging obstruction to right atrial emptying, i.e. tricuspid stenosis. A very rapid y descent on the other hand is considered strong evidence against the presence of an organic tricuspid stenosis. The right atrial pressure curve in our case showed a predominant a wave of 24 mmHg, v wave of 20 mmHg, and a y descent to 14 mmHg. On deep inspiration a distinct deepening and steepening of the y descent down to 2 mmHg occurred (Fig. 1b). A steep y descent is seen in severe tricuspid regurgitation but the absence in our case of a tall dominant v wave rules out this possibility.

Sannerstedt *et al.* (1962) pointed out that the most significant haemodynamic findings in right atrial myxoma are to be sought during the phase of rapid filling, consisting of irregularities of the right atrial pressure curve during this phase. They suggested that these changes could be the result of intermittent occlusion of the tricuspid orifice by the tumour mass.

The steep y descent seen in our case during deep inspiration indicates a prolapsing type of right atrial myxoma. In this prolapsing type of myxoma part of the tumour moves during early diastole through the tricuspid valve and away from the right atrium, causing thereby a diminution in the right atrial pressure curve. This change in the right atrial pressure curve became especially accentuated during deep inspiration, causing a very steep y descent. Changing character of the y descent indicates that obstruction to the right ventricular inflow is not the result of a static and unchanging stenosis but of a changing dynamic type of obstruction. This changing configuration of the y descent should arouse suspicion of a pedunculated type of right atrial myxoma prolapsing into the right ventricle.

The haemodynamic features described here might be helpful in differentiating right atrial myxoma from 'false positive' angiographic filling defects caused by streaming and also from other space-occupying lesions of the right atrium, such as large thrombi or filling defects caused by compression of the right atrial wall from without.

The authors thank Dr. Haran Peleq who performed the operation.

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British Heart Journal, 1977, **39**, 581-585

Homograft replacement of aortic valve and ascending aorta in a patient with non-specific giant cell aortitis

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A case of giant cell aortitis causing ascending aortic aneurysm associated with aortic regurgitation is reported. The aneurysm was excised and the aortic valve replaced using a fresh homograft. The patient has been followed up for three and a half years. There is good evidence of correction of the haemodynamic lesion and no evidence of further arteritis or aneurysmal formation. The pathological and clinical problems of this disease are discussed.

Giant cell aortitis is a rare cause of aortic aneurysm. Histological features are similar to those encountered in temporal arteritis and consist of medial inflammatory changes with destruction of the muscular and elastic fibres of the aortic wall. A striking feature of the inflammatory infiltrate is the presence of multinucleate giant cells, usually of Langhans type.

Since it may not be clinically evident, the diagnosis of giant cell aortitis is often first made by the histopathologist after necropsy or operation.

The purpose of this paper is to describe a patient with giant cell aortitis, with resultant ascending aortic aneurysm and aortic regurgitation treated by excision of the aneurysm and homograft replacement of the aortic valve with reimplantation of the coronary ostia into the Dacron graft. The clinical and pathological features of this disease are discussed.

Case report

A 61-year-old man was admitted to Harefield Hospital because of increasing dyspnoea and an aortic murmur. There was no family history of heart disease. The patient was well until 1970 when he began to hear noises in the ears which were synchronous with the pulse. Since then he had been increasingly conscious of fatigue and thought he was slightly short of breath, especially on stooping. He had no polymyalgia, headache, or chest pain. In 1972, on a routine medical examination, a heart murmur was heard. There was no history of rheumatic fever or venereal disease. He was known to have had a peptic ulcer which gave rise to occasional bleeding.

On examination the jugular pressure was normal, the pulse regular at a rate of 82 a minute and of collapsing type. All pulses were palpable, with prominent carotid pulsations in the neck. The blood pressure was 160/60 mmHg. There was left ventricular enlargement grade 3/4. Both heart sounds were present, and in the aortic area an ejection systolic murmur grade 2/4 and an early diastolic murmur grade 2/4 were heard. Physical examination otherwise showed no abnormalities.

Laboratory tests showed negative serology for syphilis. The ESR was 4 mm (Westergren). An electrocardiogram showed QRS frontal axis of −30°, sinus rhythm and evidence of left ventricular hypertrophy. The chest *x*-ray picture indicated cardiomegaly with left ventricular configuration. Cardiac catheterisation (right and left) showed a mean wedge pressure of 6 mmHg with an *a* of 2 and *v* of 9; pulmonary arterial pressure 24/5 mmHg; aortic pressure 150/65 mmHg, with no gradient across the aortic valve. Cardiac index was 1·8 l/min per m^2 with a pulmonary vascular resistance of 2 units. Aortography defined an aneurysm involving the proximal ascending aorta and grade 3/4 aortic regurgitation. The upper margins of the sinuses of Valsalva were not clearly defined. Left ventriculography suggested moderate impairment of left ventricular contractility.

The operation was performed using a median sternotomy and employing standard cardiopulmonary bypass with coronary perfusion. A large aneurysm of the ascending aorta involving the sinus region was present. On opening the aneurysm, the aortic valve which was bicuspid in configuration, was grossly regurgitant. The valve was resected and replaced with a fresh 'unstented' aortic homograft. The aneurysm was excised and the aortic continuity was restored using a 30 mm preclotted Dacron tube, 5 cm in length, followed by reimplantation of both coronary arteries. Examination of the resected piece of aorta, which measured 10 × 6 cm and was slightly thickened, showed multidirectional intimal wrinkling. The resected aortic valve consisted of the fused two coronary cusps, which were 3 cm long, with a calcified ridge along the middle and the non-coronary cusp which measured 2 cm in length and was thin.

Microscopically there was distinct old mesoaortitis with scarring, a few chronic inflammatory cell foci, and adventitial thickening with perivascular cuffing by lymphocytes and plasma cells. The intima was irregularly thickened with fibrin deposition on the endothelial surface and atheroma superimposed. Mild cystic medial degeneration was also present in the media. The block from the proximal aorta showed, in addition, a central zone of degenerate looking media bordered by giant cell granulomata (Fig. 1 and 2). There was little medial mucoid change in this piece. The cusps of the aortic valve showed only moderate nodular fibrous thickening at their margins.

After operation the patient made satisfactory progress and was discharged 2 weeks later. Because of his peptic ulcer he was not given steroids. Three and a half years after the operation the patient was well and asymptomatic with normal pulse and blood pressure (160/90 mmHg). On auscultation there was a soft systolic murmur and a soft early diastolic murmur in the aortic area. There were no clinical or

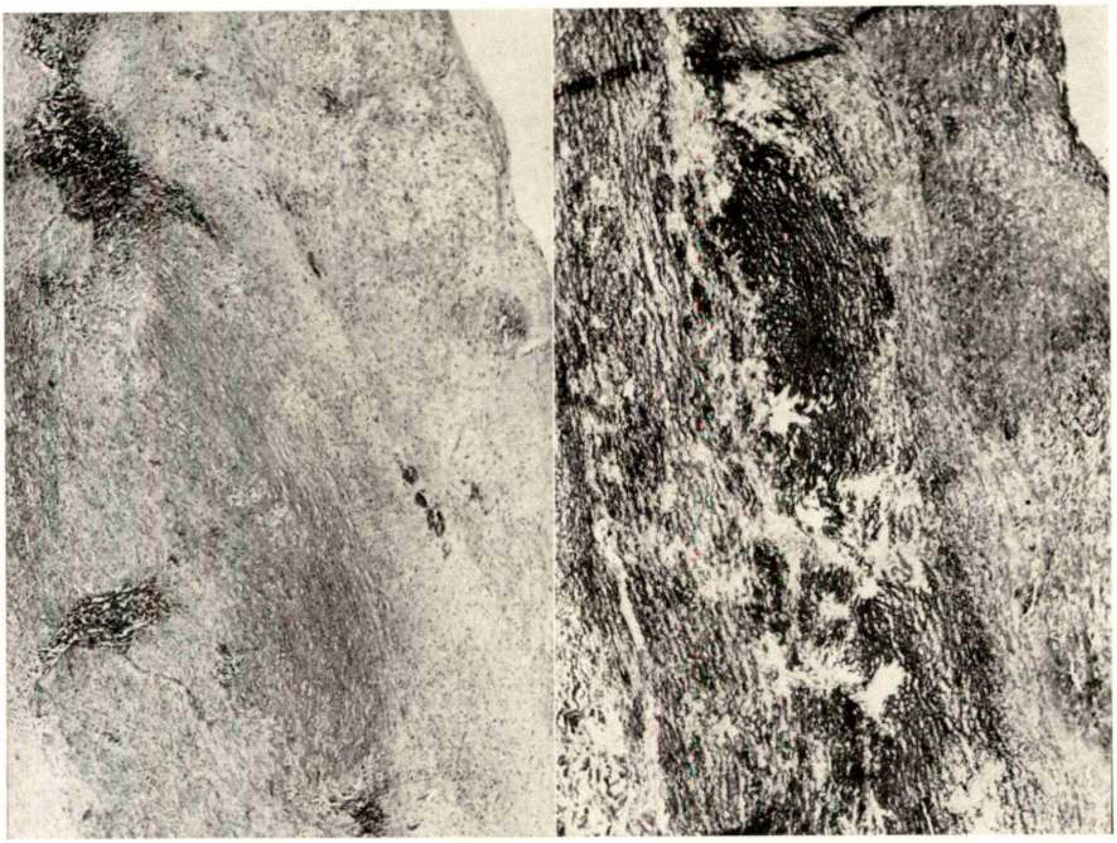

Fig. 1 *Section from proximal aorta showing well demarcated eosinophilic areas of degeneration in media and focal inflammatory cell infiltration [(a) Haematoxylin and eoxin; (b) Weigert elastic-van Gieson; both ×25].*

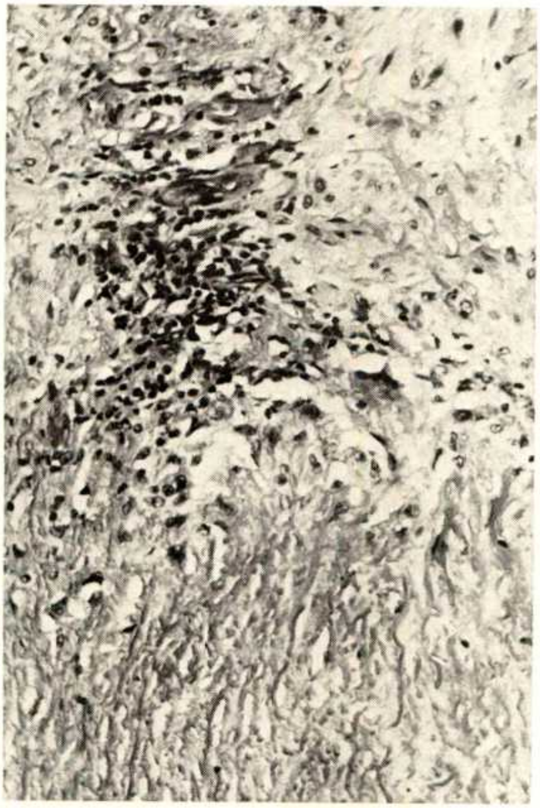

Fig. 2 *Higher power view of the inflammatory infiltrate upper margin, showing several multinucleate giant cells among the mononuclear cells. (Haematoxylin and eosin ×165.)*

radiological abnormalities in the chest and the electrocardiogram showed sinus rhythm with mild left ventricular hypertrophy. Left heart catheterisation and coronary and renal angiography were performed in order to assess the possible involvement of such arteries. A cineangiocardiogram indicated a well-contracting left ventricle, with a slightly raised end systolic volume. The aortic root injection confirmed only a minimal trace of aortic regurgitation with a Dacron graft in place. The arch and the descending thoracic aorta were normal. Coronary and renal angiograms were normal.

Discussion

Aortitis with giant cells can occur in some infective conditions, notably syphilis and tuberculosis, as well as in rheumatoid arthritis, Reiter's syndrome, scleroderma, and ankylosing spondylitis (Marquis *et al.*, 1968; Hudson, 1965–70). The aorta is also one of the vessels commonly involved in giant cell arteritis (Sproul and Hawthorne, 1937; Cooke *et al.*, 1946; Magarey, 1950; McMillan, 1950; Bettez and Delorme, 1970).

In addition, infarct-like lesions surrounded by chronic inflammatory cells and giant cells may be found limited to the aorta and great vessels (Heggtveit *et al.*, 1963) in the condition referred to as 'idiopathic medial aortopathy' (Marquis *et al.*, 1968).

Whatever the aetiology, the aortic medial inflammation and necrosis will ultimately result in scarring of the media with loss of its elastic properties. The affected aorta tends to enlarge and, according to Laplace's law, is more liable to formation of aneurysm. If hypertension is present, dissection can take place (Harris, 1968; Grivaux *et al.*, 1973), with possible rupture and sudden death (Ainsworth and Gresham, 1961; Garret, 1963). Bettez and Delorme (1970) in a review of the reports on giant cell aortitis found moderate aortic dilatation in only 5 of 29 collected cases, while an aneurysm developed in 24 with 2 cases of fatal rupture. The lesion was localised in the thoracic or abdominal aorta in 17 cases, while in 12, other arteries were also affected.

The uncomplicated lesion is silent and can be detected only microscopically at necropsy. When significant dilatation or aneurysm of the ascending aorta occurs, the clinical picture is dominated by the signs of aortic regurgitation resulting from distortion of the aortic valve, as in our patient.

The clinical diagnosis of giant cell arteritis with aortic involvement, though difficult, can be suspected in case of rapidly evolving aortic regurgitation associated with temporal arteritis or polymyalgia in patients with negative serology, a raised ESR, and no history of rheumatic fever. The diagnostic value of concomitant temporal arteritis is not in doubt. Harris (1968), in 11 cases of dissecting aneurysms associated with giant cell aortitis, found a positive history of temporal arteritis in 5.

Our patient presented with the signs of aortic regurgitation without a history suggesting temporal arteritis, and temporal artery biopsy had, therefore, not been performed. Serology for syphilis was negative and ESR normal. There had been no symptoms suggesting polymyalgia or other collagen disease. Though we cannot exclude the possibility that the aortitis was part of a giant cell arteritis we feel that the diagnosis is most likely to be the form of isolated giant cell aortitis, a subgroup of idiopathic medial aortopathy of Marquis *et al.* (1968). Surgical treatment of giant cell aortitis has been reported only on few occasions. The first concerned a 30-

year-old Negro woman with an aneurysm of the proximal ascending aorta associated with severe aortic regurgitation (Austen and Blennerhassett, 1965). At operation the aortic intima showed small white nodules while the aortic valve was normal. The aneurysm and aortic valve were excised and replaced by a Starr prosthesis, aortic continuity being restored with a Teflon graft. The diagnosis was made postoperatively on the basis of the microscopical findings. The patient was followed for 6 months during which time she remained well. Kent and Arnold (1967) excised a dissecting aneurysm of the descending thoracic aorta in a 35-year-old man who had complained of haemoptysis associated with productive cough and chest pain. At operation multiple raised nodules, varying in diameter from 1 to 15 mm, were found in the aorta. The diagnosis was also made microscopically. The postoperative course was complicated by myocardial infarction, probably resulting from involvement of coronary arteries. At follow-up 5 months later, dyspnoea and angina were present on exertion but the radiographic appearances of the heart and mediastinum were normal.

Zumbro, Henley, and Treasure (1975) have reported the case of a 7-year-old Korean boy who underwent successful surgical excision of saccular aneurysm of the ascending aorta. There was no past history of trauma or infective diseases. Chest *x*-ray film had been normal one year previously. The aneurysm was discovered on a routine chest film taken because of respiratory infection and removed by lateral aortorrhaphy with cardiopulmonary bypass. The patient remained well during the 6 months of follow-up.

In our patient surgical correction was accomplished by the excision of the aneurysm and aortic valve, followed by insertion of an aortic valve homograft. Aortic continuity was restored using a Dacron tube with reimplantation of both coronary arteries. The homograft was fixed in place by two suture lines, with a technique similar to that described by Barratt-Boyes (1965), Ross (1968), and Ross and Yacoub (1969), and the top of the homograft was fixed to the Dacron tube. At operation the aortic intima did not show the nodular lesions seen by Austen and Blennerhassett (1965) and Kent and Arnold (1967).

The diagnosis was based on the histological findings of necrotic areas and meso-aortitis with giant cells. Follow-up for three and half years has shown no evidence of progressive disease.

In patients with temporal arteritis the use of steroids has been suggested in order to prevent possible progression of the disease (Harris, 1968). None of the patients treated surgically had been on steroids after operation, and there was no evidence of progress of the disease during the period of follow-up which varied from 5 months (Kent and Arnold, 1967) to 3½ years (present case). In addition our patient gave a history of peptic ulcer which we felt was a contraindication to long-term steroid therapy.

Despite his aortitis and aneurysm which are regarded by many workers as a contraindication to the use of homograft, our patient, 3½ years after the operation is well and the homograft is functioning efficiently. However, the late prognosis of patients with giant cell aortitis is still unknown and only regular clinical and radiological follow-up will give a better understanding of the course of the disease.

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Notices

British Heart Journal, 1977, **39**, 586

European Symposium on Paediatric Cardiology

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The XIII World Congress of the International Cardiovascular Society will be held at Keio Plaza Inter-Continental Hotel from Tuesday 30 August to Friday 2 September 1977.

Information from secretariat:

3–23, 7 Chome,
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Minato-ku,
Tokyo 106,
Japan.

First International Congress on Cardiac Rehabilitation

First International Congress on Cardiac Rehabilitation under auspices of Council on Rehabilitation of the International Society of Cardiology, Hamburg, 12 to 14 September 1977.

For further information write to the secretary of the congress: Prof. Dr. med. Kurt König, Herz-Kreislauf-Klinik Waldkirch, Kandelstrasse 41, Postfach 270, Phone: 07681/8035–39 D 7808 Waldkirch.

International Symposium on Diagnosis and Treatment of Cardiac Arrhythmias

An International Symposium on the diagnosis and treatment of cardiac arrhythmias will be held in Barcelona on 5–8 October 1977, organised by the Spanish Society of Cardiology under the patronage of the European Society of Cardiology.

Further information can be had by writing to The General Secretariat of the Symposium, Arpatado de Correos 22.055, Barcelona (Spain).

The Future of Cardiology in Asia

The Second ASEAN Federation of Cardiology Congress will be held from 19–22 October 1977 at the Philippine Plaza Hotel, Manila, Philippines. The Congress will be under the auspices of the Philippine Heart Center for Asia with the Philippine Heart Association, Department of Foreign Affairs, Department of Health, and Department of Tourism as co-sponsors.

A variety of subjects relating to coronary artery disease, hypertension, congenital heart disease, cardiac pacing, and valvular heart disease will be presented. The deadline for abstracts is 31 August 1977.

For additional information concerning papers, exhibits, and registration forms, please write to: *The Secretariat,* Second ASEAN Federation of Cardiology Congress, East Avenue, Quezon City, Philippines.

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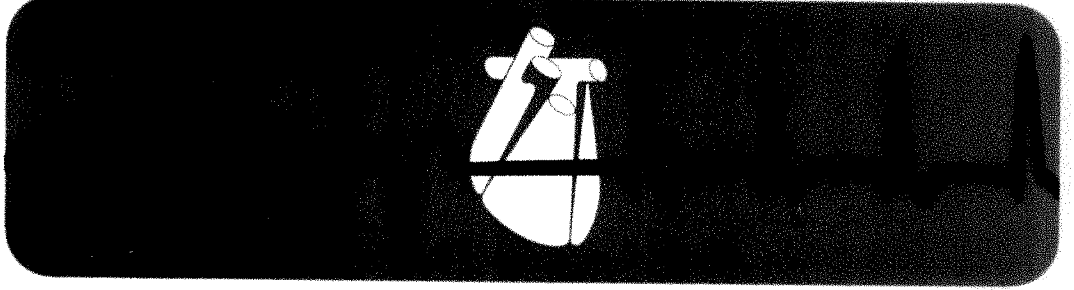

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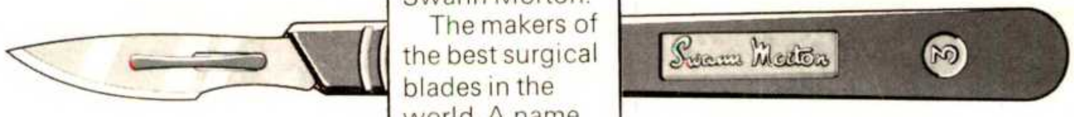

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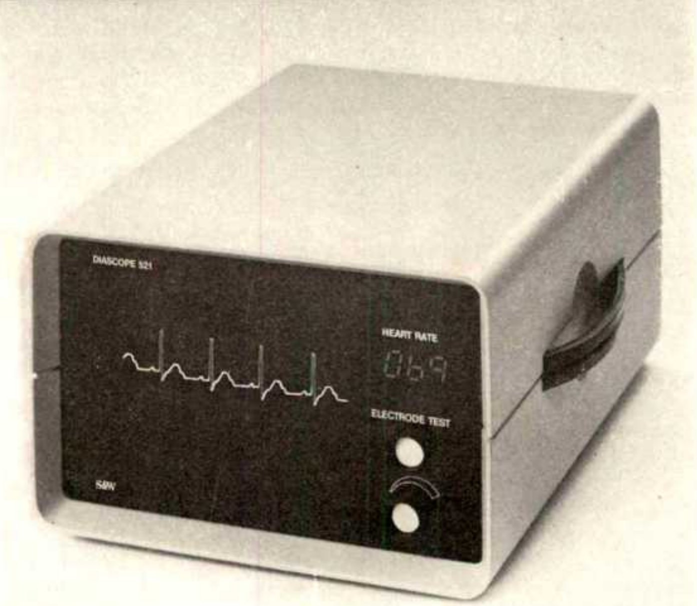

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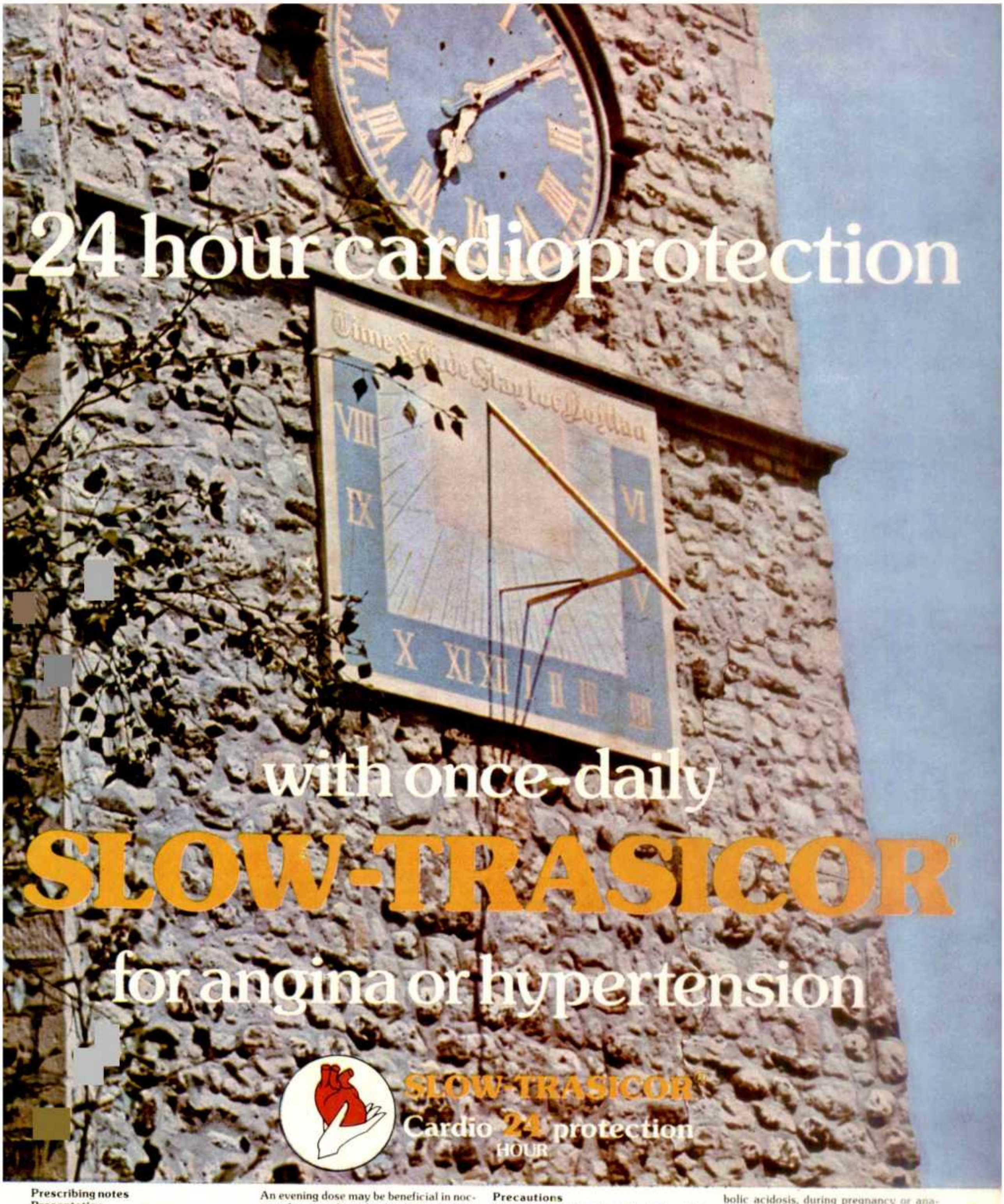

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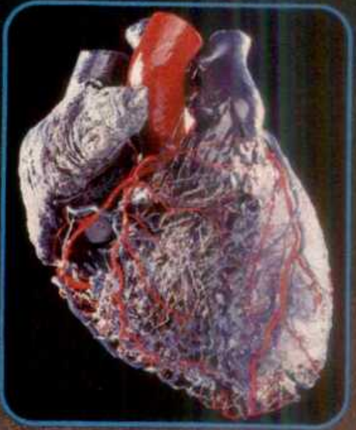

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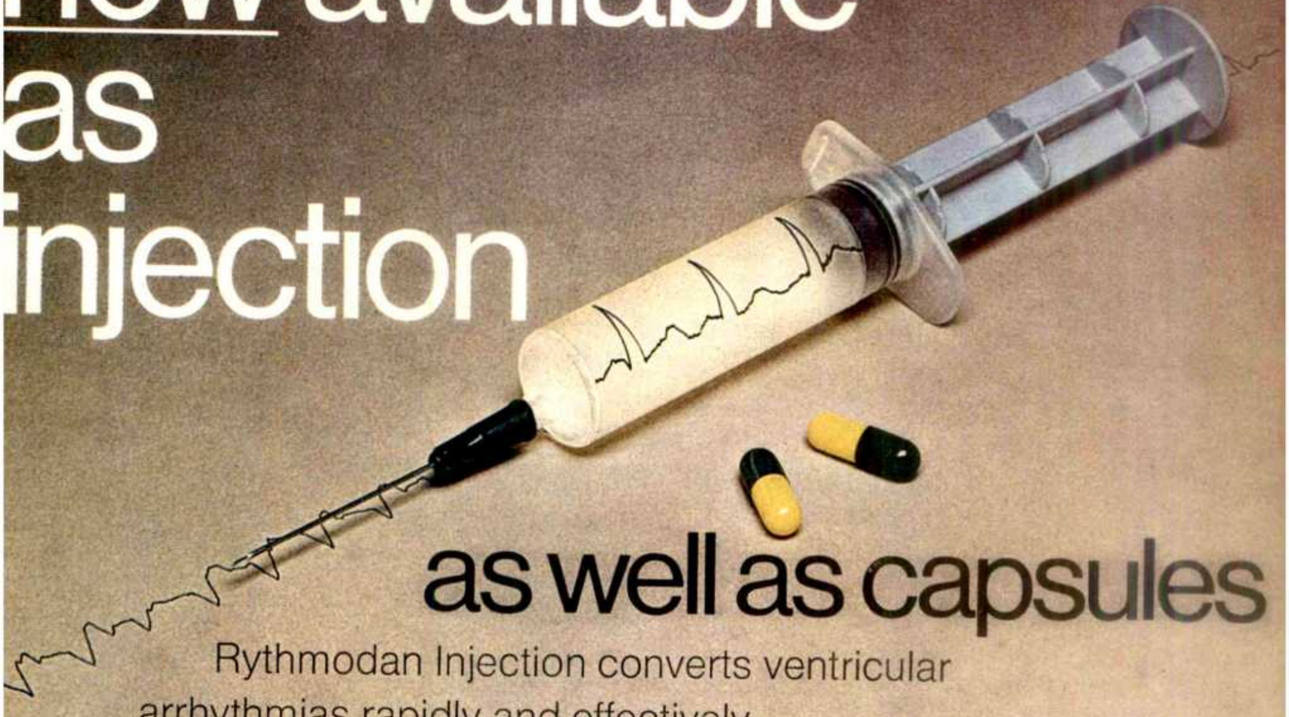

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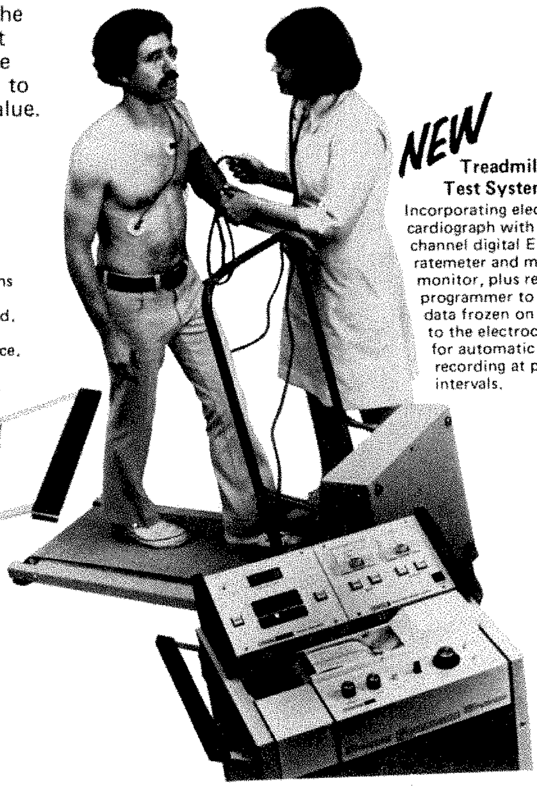

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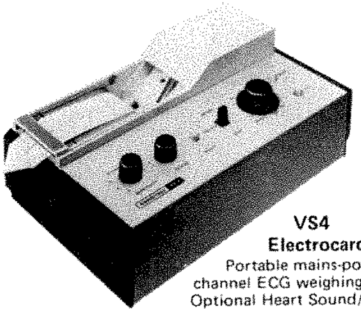

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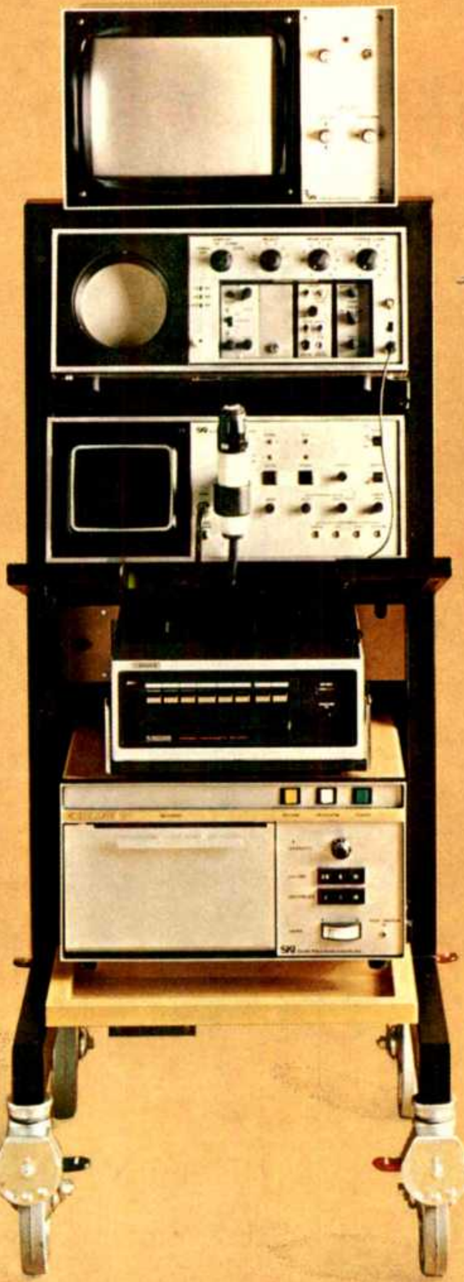

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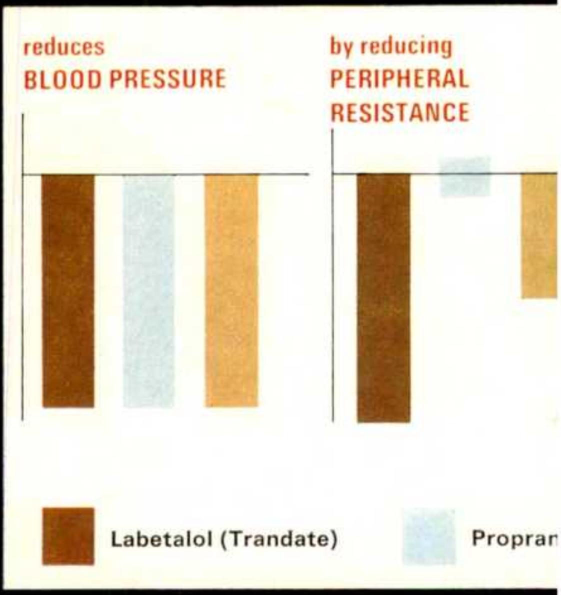

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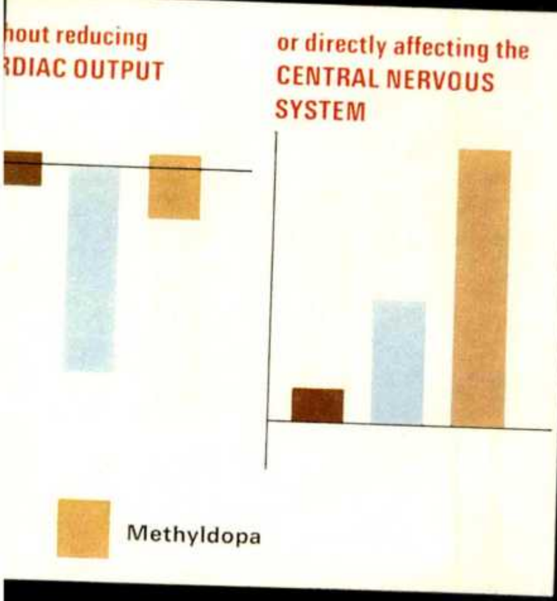

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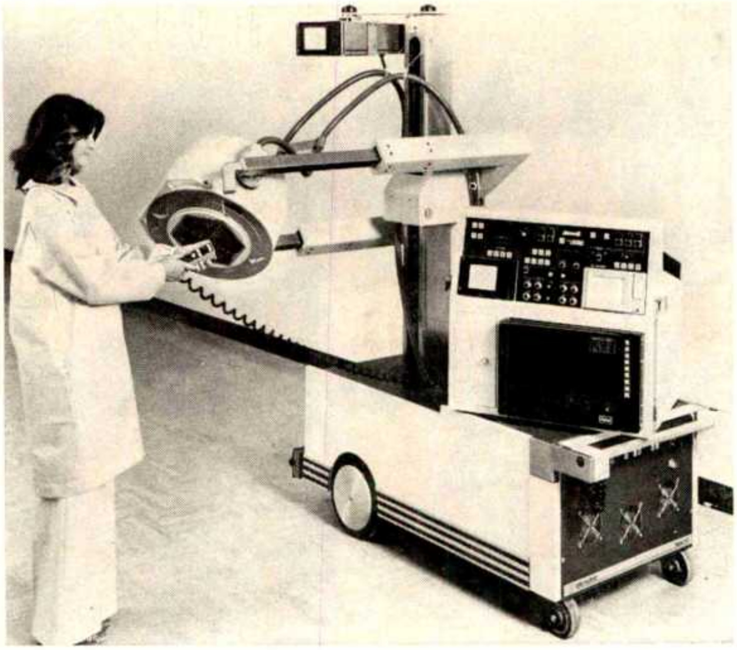

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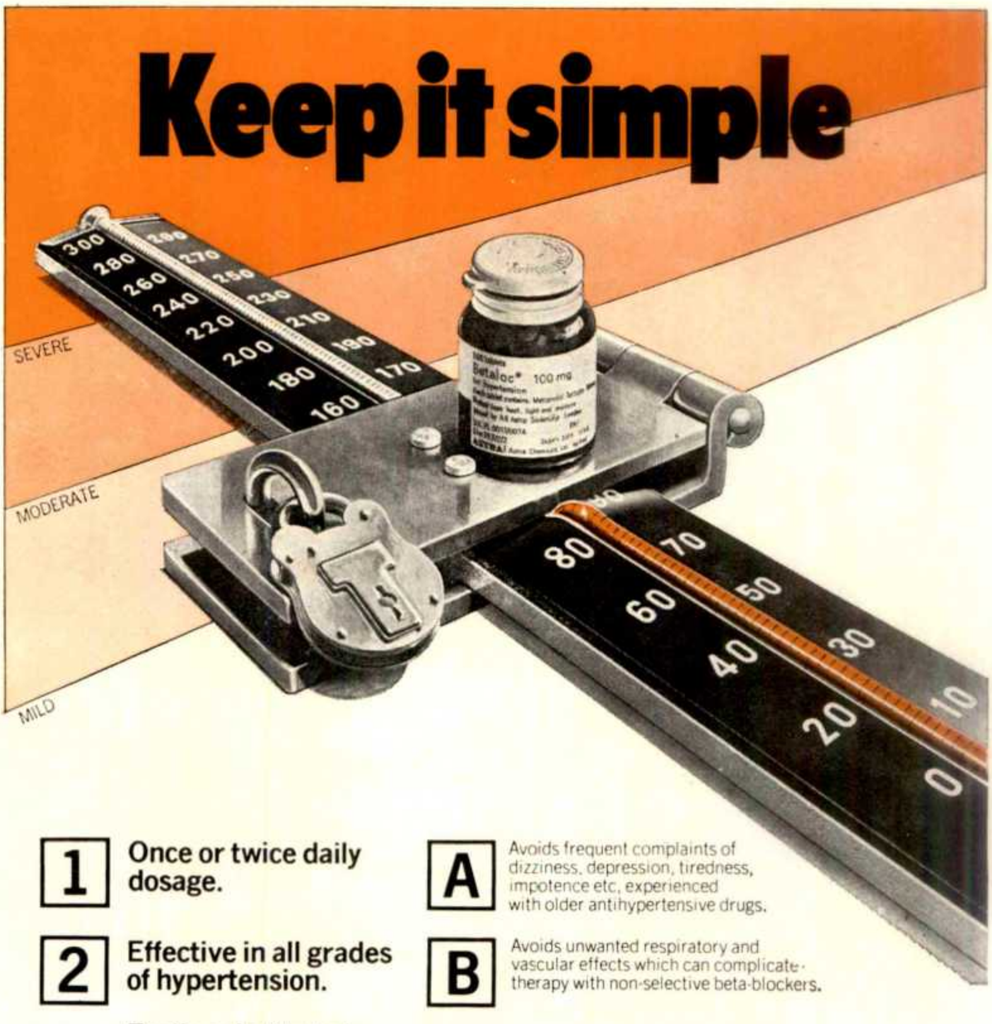

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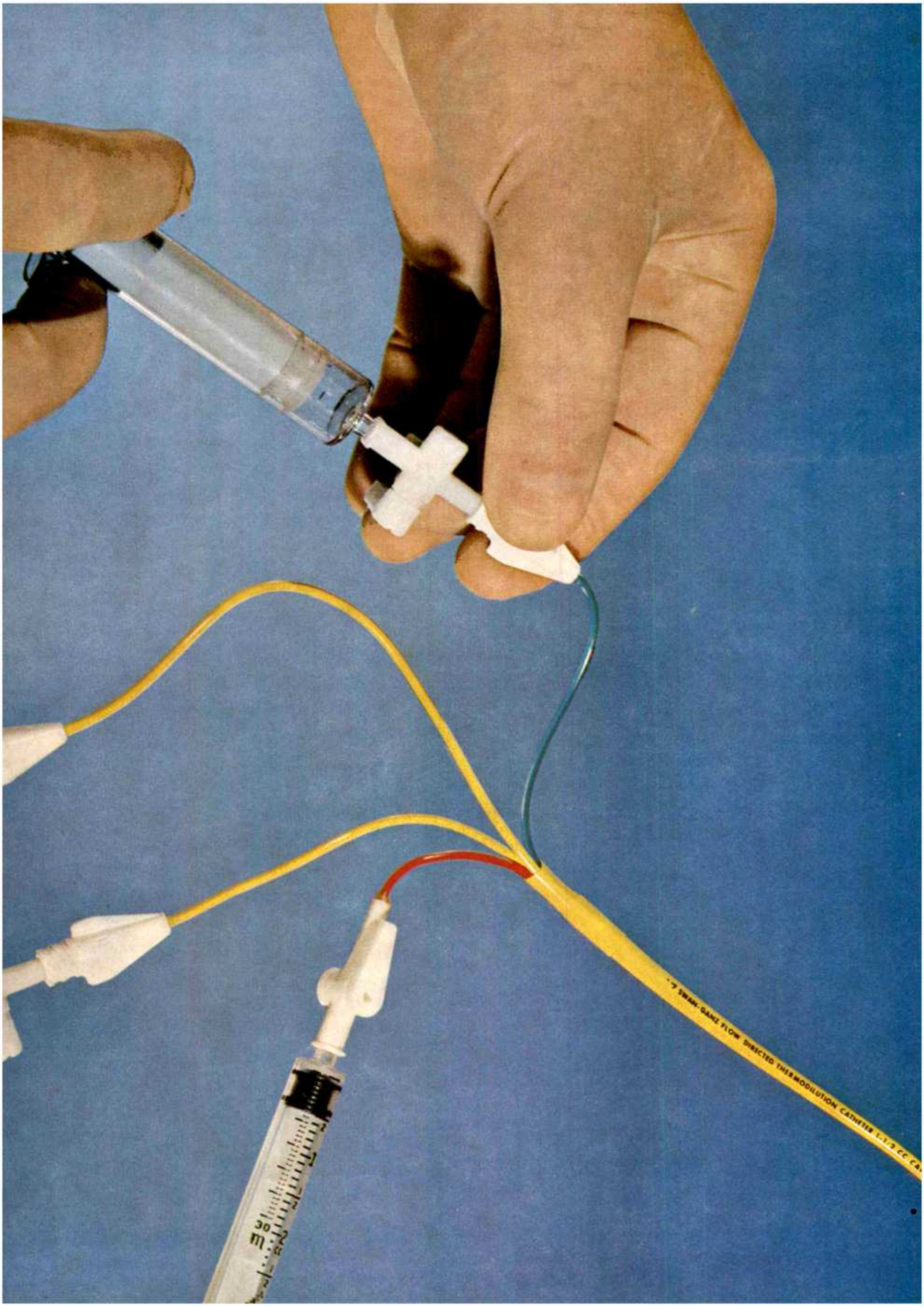
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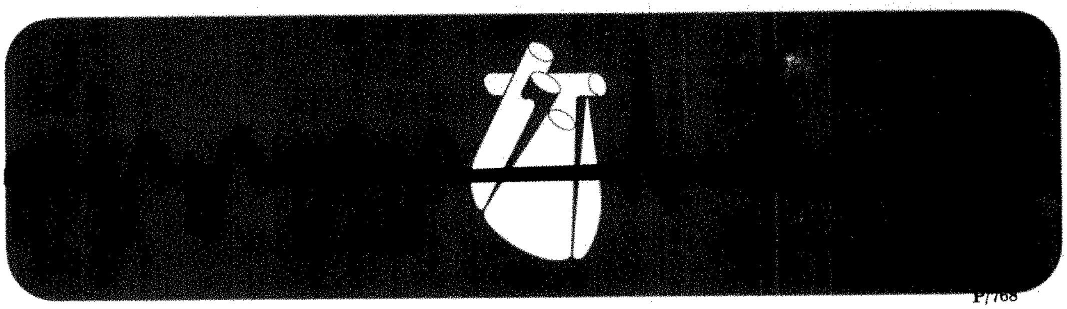

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Editorial

British Heart Journal, 1977, **39**, 587–593

Psychological methods in treatment of hypertension: a review[1]

ANDREW STEPTOE[2]

It has been shown in recent years that the blood pressure of most hypertensives can be regulated successfully with drugs (Freis, 1967, 1970). Nevertheless, there are circumstances in which alternative methods of management are attractive. Hypotensive agents frequently produce unpleasant side effects. Bulpitt and Dollery (1973) found that a substantial number of patients complained of sleepiness, weakness of the limbs, or postural hypotension, and it appears that few of the drugs in common use are completely free of such complications (Page *et al.*, 1976). There is also the problem of compliance with treatment. Blackwell (1973) has estimated that over 25 per cent of outpatients do not take prescribed drugs regularly; this is most likely to occur with patients on long-term treatment or taking more than one drug. Both these factors are common in the management of essential hypertension.

Even when patients are under treatment, the regulation of blood pressure is not always satisfactory (Langfeld, 1973). Taguchi and Freis (1974) observed that a considerable proportion of the patients who entered the Veterans Administration study with diastolic pressure levels between 90 and 114 mmHg did not show reductions below 90 mmHg during active treatment. Doubts about the effectiveness of drug therapy for diastolic pressures under 105 mmHg have recently been discussed by Short (1975). Problems with drug therapy may be particularly disturbing in the case of younger hypertensives, since many are faced with the prospect of very long-term medication for an asymptomatic condition.

Recent interest in the psychological regulation of blood pressure has been focused on two methods of voluntary control. The first, known as 'biofeedback', has evolved from research in both man and animals on the instrumental conditioning of visceral and autonomic functions (Miller, 1969). The patient is provided with information feedback of blood pressure and so is made aware of fluctuations in the level. Regular or continuous monitoring of pressure is required in order to maintain the feedback loop. With such training, the patient may learn to regulate the pressure level and ultimately to reduce it. Exteroceptive feedback of either systolic or diastolic blood pressure can be given, depending on the monitoring techniques available. The second method of control depends on instructing people in relaxation or meditation; compliance with these instructions may lead to deep relaxation of skeletal musculature, together with reduced arousal of the autonomic nervous system. This latter approach will be termed 'instructional' in this review; despite wide variations in the methods by which relaxation and meditation are induced, all such procedures are characterised by programmes of verbal instruction. It has been argued that many techniques such as yoga, hypnosis, transcendental meditation, and zen, may be grouped together since they lead to similar hypometabolic states (Benson *et al.*, 1974a).

There is some difference in the type of voluntary control achieved using biofeedback on the one hand, or instructional methods on the other. Exteroceptive feedback is used to train subjects in the direct control of blood pressure, and this can include both increasing and decreasing the level. Relaxation and meditation produce reductions in autonomic arousal of which blood pressure changes are only one manifestation. In consequence, feedback procedures may lead to specific changes in blood pressure that are relatively independent of other cardiovascular and physiological adjustments, in contrast to the general effects of instructional techniques. It should also be pointed out that while instructional procedures can be simply and economically applied, biofeedback requires instrumentation for continuous or semicontinuous blood pressure monitoring.

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[1] The author acknowledges the support of the Medical Research Council, U.K.

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The effects of both biofeedback and instructional techniques in lowering blood pressure are being investigated in patients with essential hypertension. It is inevitable that in a rapidly expanding field of this kind, a review of the current status of treatments cannot be regarded as definitive. Nevertheless, it is hoped that trends emerging from these studies can be identified, and that readers will be able to evaluate the usefulness of the techniques.

Size of effects

The assessment of psychological treatments must take into account the modifications which can be produced with drugs, together with the magnitude of responses that can be considered clinically significant. For example, Freis (1970) reported that patients starting treatment with diastolic blood pressures between 90 and 114 mmHg showed average reductions in systolic and diastolic pressure of 27·2 and 17·4 mmHg, respectively. Greater effects are seen in patients with higher initial pressure. However, Taguchi and Freis (1974) found that a proportion of patients responded only moderately to antihypertensive medication, but nevertheless sustained a reduced rate of morbid events similar to that in patients who showed large pressure reductions. In this group of poor responders the average decrease in diastolic blood pressure was only 7 mmHg. Dorph *et al.* (1970) classified patients into good and poor responders according to the extent to which blood pressure remained above the normal limits for each age group. No difference was found between patients in the two categories in relation to a number of visceral signs of pathology It can thus be argued that while large changes in blood pressure are desirable, clinically valuable effects may result from comparatively small reductions.

Non-specific factors

Blood pressure is extremely sensitive to external influences. Factors such as clinical attention and an enthusiastic approach to treatment can lead to dramatic blood pressure reductions. Goldring *et al.* (1956) 'treated' hypertensive patients with an impressive electronic gun, having led patients to expect much of the procedure. Decreases in blood pressure of up to 38/27 mmHg were found, though full responses frequently did not occur for several weeks. Similarly with oral placebos, reduction in blood pressure from 222/128 to 176/112 mmHg has been reported, a significant effect being maintained for over 6 months (Grenfell *et al.*, 1964).

On the other hand, the influence of placebos may have been exaggerated, and confused with other causes of blood pressure fall. The greatest decreases in blood pressure observed by Goldring *et al.* (1956) occurred during the pretreatment stabilisation phase in hospital. Likewise, Moutsos *et al.* (1967) found that many of the effects of drug placebos, including apparent 'dose related' responses, were primarily a function of the duration of hospital stay.

It is probable that any instructional or feedback programme for blood pressure reduction will involve these non-specific factors by generating high expectations for new, vigorously pursued treatments. The resulting reductions cannot be distinguished from the true effects of the treatment unless a control group is given a placebo with equal expectations and the same amount of clinical attention. Thus studies confined to a single group of patients receiving the 'active' treatment do not provide convincing evidence for the value of that procedure. It will be apparent that many of the reports of psychological approaches to the treatment of hypertension fall into this category.

I will not attempt to discuss all the reports of voluntary blood pressure control in hypertensive patients. Several describe laboratory studies which do not include adequate pretreatment assessment or follow-up data. A number are methodologically unsound, first in the use of unsatisfactory blood pressure measurement protocols and secondly in the failure to allow sufficient time for patients to adapt to repeated blood pressure measurements and to the laboratory setting. It is well known that blood pressure recorded in the clinic or laboratory will fall during the course of several sessions, and such a trend can be mistaken for an effect of treatment (Dunne, 1969; Benson *et al.*, 1971; Brady *et al.*, 1974).

Biofeedback methods

It has been found in a number of laboratories that normotensives can raise or lower systolic and diastolic blood pressure using feedback techniques, and there have been some investigations of the mechanisms involved (Brener, 1974; Steptoe, 1976). Kristt and Engel (1975) have shown that voluntary control can also be acquired by hypertensives. Five patients with long histories of high blood pressure were trained intensively with feedback, and all showed that they were able to raise and lower systolic pressure. This ability was maintained even after several weeks without laboratory training.

Hypertensive patients have been investigated in a number of other studies. Benson *et al.* (1971) studied 7 patients on a number of occasions, care being taken to allow for complete adaptation to the laboratory and measurement procedures before contingent systolic pressure feedback was introduced. Systolic blood pressure was reduced from a postadaptation average of 164·9 mmHg to 148·4 mmHg at the end of training, the fall in blood pressure varying from 0 to 33·8 mmHg. Diastolic pressures were not recorded, and no follow-up data were reported, so the authors were justifiably cautious in ascribing therapeutic value to the procedure. No control group was included.

Goldman *et al.* (1975) treated 7 unmedicated hypertensives with systolic pressure feedback, and compared them with 4 patients who attended blood pressure measurement sessions alone. By the beginning of the ninth session, blood pressures were reduced from an average of 167·4/108·6 to 161·1/93·9 mmHg, a change which was significant for diastolic pressure only. In contrast, the blood pressure in the control subjects altered from 154·4/98·9 to 157·0/94·5 mmHg. Significant within-session reductions in systolic pressure (average 7·0 mmHg) were also observed in the feedback group. No follow-up data were reported. The diastolic pressure reductions observed in this study are particularly impressive, with falls in pressure ranging from 5 to 35 mmHg. Unfortunately, a number of features in the design make this result difficult to interpret. The blood pressures recorded at the beginning of each session were taken by conventional sphygmomanometry, and the authors do not state that the observer was unaware of whether patients were in control or treatment groups; this practice can lead to bias and error (Wright and Dore, 1970). There were no pre-training sessions to allow for adaptation and it is possible that some of the pressure reductions were a result of this factor. The control group only attended for 3 sessions, but even in this time showed an average reduction in diastolic pressure of 4·3 mmHg. The two groups showed a difference in initial blood pressure and may therefore not be comparable. It is also disturbing that significant reductions were seen in diastolic but not systolic blood pressure, even though the latter was the pressure that patients were learning to control.

A further controlled study has been reported by Richter-Heinrich *et al.* (1975). Thirty untreated mild hypertensives, with an average initial systolic pressure of 144 mmHg, were investigated in a short 4-session experiment. Ten of the patients acted as 'yoked controls'; that is the pressure feedback which they received was derived from another subject and not from themselves, so that the effect of the conditioning procedure *per se* could be discovered. Both between-session and within-session reductions in blood pressure were observed, and these were consistently greater in the true feedback condition. On the fourth day, the presession systolic pressure averaged 123 mmHg in this group. Although this experiment was brief, with no adaptation period or follow-up data, there are a number of features which should be mentioned: (a) The changes in systolic pressure were not dependent on changes in diastolic pressure and heart rate, thus showing the specific nature of feedback training. (b) Patients who were classified as highly anxious on a paper and pencil test showed significantly smaller reductions in blood pressure than the less anxious individuals. (c) The feedback was provided by an automatic recorder which monitored blood pressure once a minute. This is different from the sophisticated systems for semicontinuous measurement that have been used by others, and suggests that simple, widely available equipment may be relatively effective.

This conclusion is supported by Blanchard *et al.* (1975) who gave 4 hypertensive patients relaxation instructions followed by systolic pressure feedback once a minute. Blood pressure decreases were seen in all patients during the experimental sessions. Intermittent feedback was also employed in the studies by Elder and his colleagues (Elder *et al.*, 1973; Elder and Eustis, 1975). Their results are difficult to assess, since blood pressure changes are expressed as percentage changes from the level at the beginning of treatment, and because no time was allowed for habituation or adaptation. In the study which showed positive results, patients were admitted to hospital and put on salt-free diets three days before the experiment (Elder *et al.*, 1973). No clinically significant effects of feedback training were observed by Elder and Eustis (1975) on 30-day follow-up of a mildly hypertensive outpatient group.

The studies discussed above have all used feedback of systolic pressure, and there is little evidence on the efficacy of diastolic pressure information. However, Schwartz and Shapiro (1974) briefly reported a study of 7 hypertensives who were trained with diastolic pressure feedback for 10 sessions. Only one patient responded positively. The modification of patterns of cardiovascular activity was examined by Surwit and Shapiro (1977). Borderline hypertensives were given feedback only when systolic pressure fell and heart rate slowed simultaneously, so that a reduction of general cardiovascular arousal might be generated. Reliable clinical gains were not made, but it is probable that this pattern feedback was inappropriate since patients' heart rates were not increased in the first place.

It can be concluded that clinically useful blood pressure changes with feedback have not been consistently shown. In some cases the blood pressure reductions have been substantial, but they have not been shown to persist. It is possible that efficient and lasting self-control requires rather more sessions than have commonly been employed. For example, the large effects reported by Benson *et al.* (1971) were the result of up to 32 treatment sessions.

Most of the experiments reviewed here were concerned with the demonstration of blood pressure control by hypertensives, and have not included control groups, or follow-up data or other indices of treatment effectiveness. But considerable energy is being devoted to the field, and the roles of biofeedback and the other components of training may be elucidated soon. It is probable that the relaxing laboratory conditions under which training has been carried out are not ideal. Blood pressure falls over time in such settings irrespective of the presence of biofeedback, while attention to a stimulating feedback display may militate against more profound blood pressure changes (Steptoe, 1976). The control of pressor reactions to specific conditions of psychological stress may be more fruitful than attempting to alter the blood pressure level when the patient is at rest.

Instructional methods

The instructional methods that have been studied in relation to hypertension have a number of common features. Nearly all emphasise deep relaxation of the muscles, while attention is frequently directed towards breathing movements (Beary and Benson, 1974). The subject is encouraged to repeat quietly a syllable or short word which prevents his mind from wandering. The mystical properties of this syllable are probably irrelevant to the physiological effects of a technique (Woolfolk, 1975). The rationale for employing instructional techniques in primary hypertension is that they can lead to reductions in autonomic, and particularly sympathetic, discharge. It is hoped that this will continue outside the training setting.

One popular version of the instructional method is transcendental meditation, a yoga technique adapted for Western use. In normotensives, reduction in oxygen consumption and heart rate have been observed, without changes in blood pressure (Wallace *et al.*, 1971). Despite this latter result, the technique has been applied to the treatment of essential hypertension.

Two studies of similar design have been carried out by Benson and his colleagues (Benson *et al.*, 1974b, c). In both of these studies, volunteers who were about to undergo initiation into transcendental meditation and who knew themselves to be hypertensive, were recruited. It should be pointed out that these volunteers had already chosen to learn meditation before entering the study, and were not persuaded to do so by the investigators. Repeated blood pressure measurements were taken before and after they learned the technique, and were continued for 5 to 6 months. In the first study, 14 people who were taking antihypertensive drugs were followed (Benson *et al.*, 1974b). The average premeditation blood pressure was 145·6/91·9 mmHg, and by the end of follow-up blood pressure had fallen by 10·6/4·85 mmHg. The second group of younger subjects were not on treatment, and their average baseline blood pressure was 146·5/94·6 mmHg. Significant reductions in both systolic and diastolic blood pressures were again seen, the mean change being 6·98 and 3·86 mmHg, respectively. Although these results are consistent, their general applicability is open to doubt. The patients were self-referred and atypical in wanting to learn transcendental meditation. High expectations of benefit are likely to be generated when people are being initiated into such a technique. Detailed physical examinations and medical histories are not reported, so that the origin, duration, and variability of the high blood pressure are unknown. In the study of treated hypertensives, no data concerning adherence to prescribed treatment are presented.

A study of transcendental meditation in a well-documented group of hypertensives has been reported by Blackwell *et al.* (1976). After 9 weeks of supervised meditation, 4 of the 7 patients showed significant reductions in blood pressure with no change or some increase in blood pressure in the other 3 patients. At 6 months, only 3 patients maintained these reductions in blood pressure, and some of these effects were contaminated by alterations in drug treatment. The authors concluded that only 2 out of the sample showed sustained decreases, with falls in blood pressure of 13·0/8·2 and 18·0/14·3 mmHg. This report indicates that transcendental meditation has a beneficial effect on the blood pressure of only a minority of people. One of the 'successes' had been diagnosed as hypertensive for only 2 months before treatment, and was not typical of the group studied. Recently, Pollack *et al.* (1977) reported that transcendental meditation had no lasting effects on blood pressure in a group of 20 hypertensives even though many reported subjective feelings of well-being. Systolic blood pressure fell significantly in the first 3 months of meditation, but by 6 months it did not differ from starting levels.

Conflicting results have emerged from experiments with instructional procedures that, while similar to transcendental meditation, are shorn of its proprietary and mystical overtones. Stone and DeLeo (1976) selected 19 young, well-motivated patients, none of whom was taking antihypertensive drugs. Five were employed as no treatment controls, while the remaining 14 underwent 5 brief relaxation sessions. After 6 months, the blood pressure of controls was unchanged, while there was a significant reduction in the treatment group. The average drop in mean arterial pressure (supine) was 12 mmHg, and 8 of the patients showed decreases of over 14 mmHg. An attempt was made to evaluate peripheral sympathetic activity by monitoring plasma dopamine-beta-hydroxylase (DβH) and plasma renin activity (PRA). The former has been suggested as an index of chronic adrenergic activity, though its use as such has yet to be firmly established (Noth and Mulrow, 1976). Reductions in both DβH and PRA were observed in the treatment group, and there were significant correlations between the decrease in DβH activity and the blood pressure fall. The fact that the patients in this study had only mildly raised pressure levels to start with (average mean arterial pressure was 110 mmHg) may have contributed to the comparatively large effects. But this is contradicted by the failure of Surwit and Shapiro (1977) to show a fall in blood pressure with a similar technique in a group of borderline hypertensives. This latter study underlines the powerful effect of the circumstances of measurement on blood pressure levels. Average pretreatment blood pressures of 156/92 mmHg were abstracted from medical notes, but in a physician's examination, levels of 170/100 mmHg were recorded. By the time relaxation therapy was introduced after 2 sessions of acclimatisation to the laboratory, average blood pressure had fallen to 137/87 mmHg. It is clear that failure to record adequate baseline measurements could lead to a completely spurious treatment result.

The last group of reports involve more complex techniques. Striking effects of autogenic training were seen in an uncontrolled trial by Klumbies and Eberhardt (Luthe, 1969). Average blood pressure falls of 35/18 mmHg were obtained in 26 patients. This study, which is only briefly described, is unusual in that over 50 patients dropped out of treatment, while of the remainder 17 were under 26 years old. Scanty reporting of baseline and measurement procedures also makes an experiment by Datey *et al.* (1969) on the effects of yoga difficult to interpret.

Further evidence for the value of yoga has emerged from the work of Patel (1973, 1975; Patel and North, 1975). A treatment package has been devised that includes lectures on blood pressure and stress, relaxation and meditation exercises, and exteroceptive feedback of muscle tension or skin resistance. It should be pointed out that biofeedback is here used as an indicator of general relaxation, rather than as a technique for specific blood pressure control. The first study by Patel (1973) will not be discussed in detail, since it has been followed by a randomised controlled trial with 34 patients (Patel and North, 1975). Treatment was carried out for only 12 half-hour sessions, during which control patients were simply asked to relax without specific instructions. Pretrial blood pressures averaged 168/100 mmHg in the treatment and 169/101 mmHg in the control group, and almost all subjects were taking antihypertensive drugs. At the end of three months' follow-up, systolic and diastolic pressures were reduced by 26·1 and 8·9 mmHg, respectively, in the treatment group, and by 8·9 and 4·2 mmHg in the control group; the difference between the groups was significant. These effects were maintained for a further six months in the treatment group, while control patients changed to the active instructional programme. They likewise responded with blood pressure reductions, coming down to the same level as the first treatment group. This study confirms the earlier results from Patel (1973), even though active treatment time was considerably curtailed. It is apparent that this programme has a substantial effect on the blood pressure of hypertensives. But high therapeutic expectations, generated by the initial meetings and the vigorous treatment, may have contributed to the size of effects in the experimental situation. Patients were encouraged to apply training in their everyday lives, and to practise relaxation and meditation regularly. This extensive active participation by patients seems to pay considerable therapeutic dividends.

Conclusions

The methods reviewed here differ widely in sophistication and duration of treatment. Comparison between them is also hampered by the variation in age, blood pressure, drug treatment, and clinical history of the patients studied. In several cases, large blood pressure reductions have been observed. However, the effects cannot be attributed solely to the biofeedback or instructional methods employed. Comparison has not been made with vigorously pursued 'pseudotherapy' with similar high expectation of benefit. Thus the contribution of non-specific placebo factors has yet to be evaluated. Nor is the mechanism of blood pressure reduction clear, since few clinical and physiological variables have been recorded apart from the blood pressure itself. Sympathetic pathways are implicated by Stone and DeLeo (1976) and by Richter-Heinrich *et al.* (1975), but more direct evidence is required.

The precise mechanism of therapeutic effects cannot be determined without measurements of variables other than blood pressure. Changes may occur in diet, exercise, smoking, and adherence to drug regimens, and these can lead to blood pressure reductions. Complete alterations in life style have been anecdotally reported by initiates into meditational practices, but few studies have recorded such behavioural data. The contribution of all these factors warrants careful investigation. Yet demonstration of their presence would not be unwelcome. Active participation by patients in a behavioural treatment will inevitably lead to many changes. Thus if adjustments in life style and diet do have effects on blood pressure, they should perhaps be explicitly encouraged in therapy. Biofeedback and instructional methods cannot be used in the same way as drug treatments, where the patient participates passively. These methods of treatment challenge patients to be the principal agents of treatment, and will not be effective without active involvement. Such methods may help to motivate patients to make the necessary adjustments in behaviour; indeed they may be valuable as components of programmes aimed at modification, not only of blood pressure, but also of other factors such as exercise and smoking, that contribute to the risk of cardiovascular disease.

It is probable that psychological treatments will be appropriate for only a proportion of hypertensives, and research into the identification of responsive individuals is required. For these people, methods of the type reviewed here may make a valuable contribution to the long-term management of high blood pressure.

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Echocardiographic findings in left ventricular to right atrial shunts

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The echocardiographic abnormalities of tricuspid valve motion in 2 patients with left ventricular to right atrial shunts are described. In both patients the abnormal anatomy was defined at surgery, in one patient the shunt being above the tricuspid valve leaflets (supravalvar) and in the other patient through the septal leaflet (intravalvar). Different patterns of tricuspid valve systolic fluttering were seen in these two cases and the possible reasons for this are discussed. After surgical closure of the defects the systolic fluttering of the tricuspid valve was no longer observed. Echocardiography appears to be useful in detecting the presence of left ventricular to right atrial shunts which otherwise may be difficult to diagnose.

The clinical diagnosis of a shunt from the left ventricle to the right atrium (LV-RA) is difficult, because the findings resemble those of an interventricular communication (Gerbode *et al.*, 1958). At cardiac catheterisation, an oxygen saturation step-up at the right atrial level, in the absence of any other features suggesting an atrial septal defect, may be confusing if the diagnosis of an LV-RA shunt has not been considered. A characteristic echocardiographic finding in this condition would, therefore, be of considerable value, not only in detecting the abnormality, but also in the appropriate planning of the diagnostic cardiac catheterisation. The present report concerns 2 patients with LV-RA shunts in whom striking abnormalities of the systolic motion of the tricuspid valve were noted. These findings amplify two previously reported cases (Nanda *et al.*, 1975) and confirm the diagnostic value of echocardiography in this condition.

Patients and methods

METHODS

The echocardiographic records were obtained using an Ekoline ultrasonoscope[1] interfaced with a Cambridge Physiological Recorder.[2] Further tracings were obtained in the second patient by interfacing the Ekoline with an Irex Multichannel Recorder.[3] The recording speed was 100 mm/s. The echocardiograms of the tricuspid valve were amplified to allow greater appreciation of the detail of valve motion. In each patient a number of echocardiographic scans were recorded to ensure that it was the anterior of two atrioventricular valves that was labelled 'tricuspid'.

PATIENTS

Case 1

This 19-year-old girl had a ventricular septal defect diagnosed at the age of 10. Though surgical closure was recommended, the patient's parents refused operation. She was lost to follow-up but now returned complaining of easy fatiguability and nonspecific chest pain. On physical examination the venous pressure was raised and the right ventricular impulse was prominent.

A loud pansystolic murmur and a low pitched diastolic murmur, interpreted as a diastolic flow murmur, were heard at the left sternal edge. Cardiac catheterisation showed a pulmonary artery pressure of 70/25 mmHg and a step-up in oxygen saturation at the right ventricular level. Dye dilution curves indicated shunts from the left ventricle to both the right ventricle and right atrium. A catheter could be readily passed from left ventricle to right atrium.

Case 2

A 33-year-old man who gave a history of a heart murmur since the age of 2 years presented complain-

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[1] Smith-Kline Ekoline 20 Ultrasonoscope Smith Kline Instruments, Inc, Palo Alto, California, U.S.A.

[2] Cambridge Medical Instruments Co., Ossining, New York, U.S.A.

[3] Irex Medical System, Mahwah, New Jersey, U.S.A.

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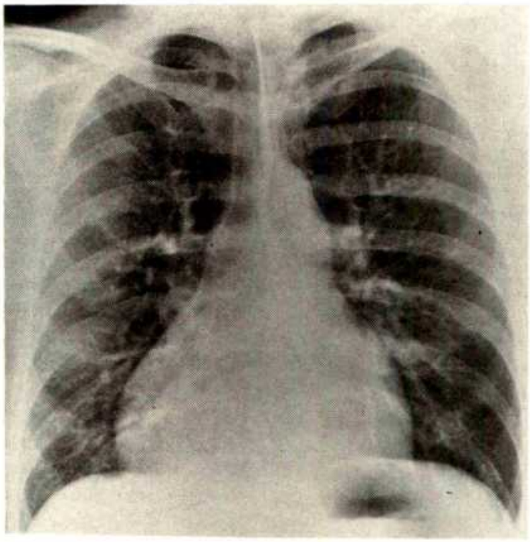

Fig. 1 *Posteroanterior chest x-ray of case 2, showing distinct prominence of the right heart border resulting from right atrial dilatation.*

ing of mild dyspnoea. On examination his venous pressure was not raised, but there was a prominent systolic pulsation to the right of the sternum. A loud pansystolic murmur was audible throughout the praecordium, prominent at both the left and right sternal edge. Chest *x*-ray examination showed striking right atrial enlargement (Fig. 1). Cardiac catheterisation revealed a step up in oxygen saturation at right atrial level. Dye dilution curves indicated a shunt from left ventricle to right atrium, and the left ventricular catheter could be passed directly into the right atrium.

Results

ECHOCARDIOGRAPHY

Case 1

The abnormal echocardiographic features of the systolic motion of the tricuspid valve are illustrated in Fig. 2. During ventricular systole the closed tricuspid valve is seen to flutter. This fluttering could be observed throughout the duration of the pansystolic murmur in early systole with the transducer in the fourth intercostal space and in late systole with the transducer in the fifth intercostal space. This abnormal systolic motion was consistently observed when the transducer was angled inferiorly from the aortic valve toward the point of tricuspid valve closure. The amplitude of the fluttering motion is approximately 3·5 cm.

Case 2

The echocardiographic findings in case 2 also showed an abnormality of tricuspid valve systolic motion and this is illustrated in Fig. 3. One of the tricuspid valve leaflets bows anteriorly into the right

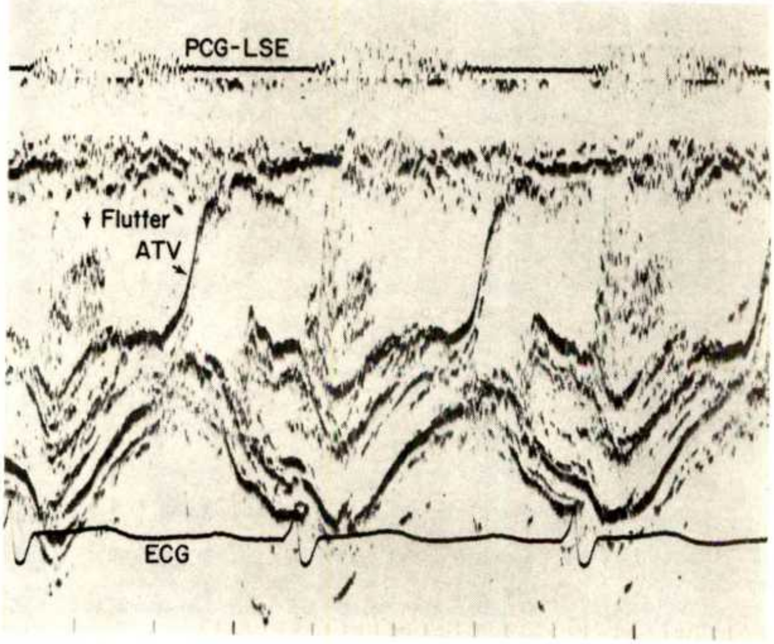

Fig. 2 *Echophonocardiogram from case 1. The anterior leaflet of the tricuspid valve (ATV) is seen opening at the start of diastole. A fluttering motion of the tricuspid valve is seen in systole. In this view the onset of the pansystolic murmur and the fluttering coincided, and in other tracings the fluttering was shown in late systole. Recording speed 100 mm/s. Time lines 0·04 s. PCG LSE—phonocardiogram at left sternal edge.*

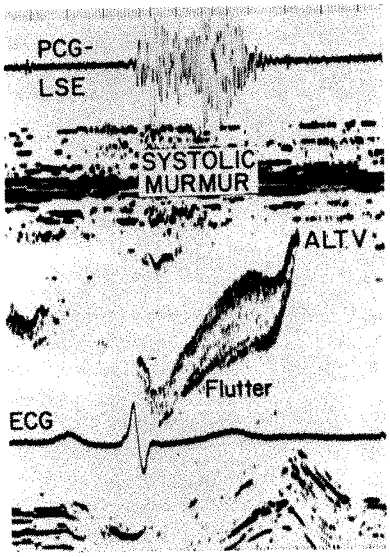

Fig. 3 *Echophonocardiogram from case 2 showing the pattern of systolic flutter of the tricuspid valve seen in the patient with a supravalvar left ventricular right atrial shunt. The fluttering coincided with the pansystolic murmur. Recording speed 100 mm/s. Time lines 0·01 s.*

ventricle and a fluttering motion is seen on the leaflet throughout the duration of the pansystolic murmur. This was consistently found on scanning from tricuspid valve closure to the aortic valve echo, the transducer angle being similar to that required to detect the systolic fluttering seen in case 1.

We have not seen these echocardiographic abnormalities in patients with an atrioventricular canal defect causing a shunt from left ventricle to right atrium.

SURGICAL FINDINGS

Case 1

A 2·5 cm membranous ventricular septal defect was identified at operation and closed with a Dacron patch. A separate LV-RA shunt was found, involving the septal leaflet of the tricuspid valve. This communication took the form of multiple small defects in the valvular tissue near its insertion into the atrioventricular ring. These were closed by direct suture. Careful echocardiographic studies in the postoperative period failed to detect any abnormality of the systolic portion of the tricuspid valve.

Case 2

The surgical findings in this patient contrasted with those in case 1. The anatomical findings confirmed the diagnosis at cardiac catheterisation of an isolated communication between the left ventricular outflow tract and the right atrium. The defect lay superior to the septal leaflet of the tricuspid valve and did not involve that structure. The communication was repaired by direct suture. The postoperative echocardiogram of the tricuspid valve was normal.

Discussion

LV-RA shunts have been previously divided into two categories—infravalvar and supravalvar (Perry *et al.,* 1949; Braunwald and Morrow, 1960; Riemenschneider and Moss, 1967). In type 1 or intravalvar, the defect involves both the membranous interventricular septum and the septal leaflet of the tricuspid valve. Since the flow of blood from the left ventricle to right atrium traverses the septal leaflet of the tricuspid valve (Fig. 4), we have chosen to call this lesion an *intra*valvar communication. In type 2 or supravalvar, the defect lies higher in the interventricular septum so that it is above the level of the insertion of the tricuspid valve (Fig. 4).

The first of the two cases reported here was of the intravalvar type, the second, supravalvar. The 2 previously reported cases of LV-RA shunts with tricuspid valve echocardiography were of the intravalvar type, though the anatomy was verified at

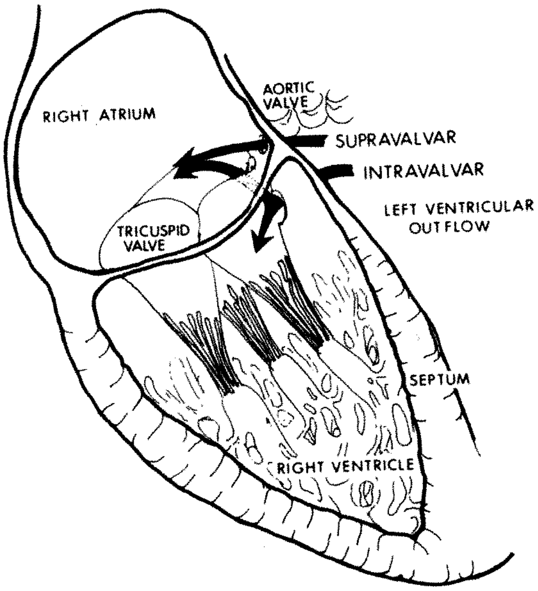

Fig. 4 *Diagram illustrating the anatomy of supra- and intravalvar left ventricular to right atrial shunts. The postulated direction of blood flow is indicated by the heavy black arrows.*

surgery in only one of these patients (Nanda *et al.*, 1975). In our patient with this defect (case 1) we found systolic fluttering of the valve, similar to that reported by Nanda *et al.*, though the amplitude of this motion was considerably greater. This increased amplitude may have been the result of the significant pulmonary hypertension present in our patient which would tend to cause right ventricular dilatation and, therefore, improve the echocardiographic recording of the tricuspid valve.

Supravalvar LV-RA shunts are less common than the intravalvar type. The systolic motion of the tricuspid valve in case 2, which was of a different pattern from that seen in the intravalvar defect, has not previously been reported. The 'flutter' seen with the supravalvar defect was of a higher frequency, being similar in appearance to that seen on the mitral valve in association with aortic regurgitation. The mechanism of tricuspid valve fluttering in LV-RA shunts is conjectural, but the following indirect evidence suggests (1) that the jet of blood impinges on the tricuspid valve in this defect and (2) that the effect of such a jet might be detected echocardiographically.

The patient described by Perry *et al.* was a child who died from bacterial endocarditis associated with a supravalvular LV-RA shunt. At necropsy vegetations were found on the septal and anterior leaflets of the tricuspid valve, suggesting that during life, the left ventricular jet of blood had impinged directly on the tricuspid leaflets. A recent report (Matsumoto *et al.*, 1976) of systolic fluttering of the tricuspid valve being seen in a patient with ruptured sinus of Valsalva into the right atrium, suggests that the effect of a jet of blood from the left heart on the tricuspid valve during systole may result in the echocardiographic recognition of tricuspid valve flutter. This is a reasonable explanation for the echocardiographic findings in our patient with a supravalvular LV-RA shunt. The different pattern of flutter in the intravalvular shunt is more difficult to explain. The lack of anterior 'bowing' may reflect the fact that during systole motion of the septal leaflet of the tricuspid valve is influenced by blood impinging on both the ventricular and the atrial aspects of the valve cusp. There would thus be no net movement of the cusp into either chamber but rather the pattern of oscillation seen in Fig. 2 would result.

After surgical closure of the defects in both our patients, the echocardiographic abnormalities of systolic motion of the tricuspid valve were no longer present. These findings show that echocardiography of the tricuspid valve may be of considerable value in the detection of left ventricular-right atrial shunts, and suggest that careful echocardiographic study of tricuspid valve motion in patients with the signs of ventricular septal defect would be of value in establishing this diagnosis. The two anatomical variations of this lesion may cause different patterns of flow through or across the tricuspid valve leaflets, hence causing differences in systolic motion of the leaflets and allowing the two variants to be separated echocardiographically.

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Intra-aortic balloon assistance in cardiogenic shock after myocardial infarction or cardiac surgery

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Sixty-eight patients were referred for consideration of intra-aortic balloon assistance, 55 of whom were accepted. Thirty-one patients were in cardiogenic shock after myocardial infarction and the remaining 24 were cardiac surgical patients. Twenty-three of the myocardial infarct group were established on IABA and all 24 of the cardiac surgical patients. Of the 23 patients with cardiogenic shock after myocardial infarction, 19 showed initial haemodynamic improvement on intra-aortic balloon assistance and 5 (22%) survived to leave hospital. Of the 24 cardiac surgical patients, 15 could not be withdrawn from total cardiopulmonary bypass. With intra-aortic balloon assistance, 11 (73%) could be withdrawn from cardiopulmonary bypass and 5 (33%) were hospital and long-term survivors. The remaining 9 surgical patients were in cardiogenic shock in the early postoperative phase, though 5 showed initial haemodynamic improvement there was only one hospital survivor in this group. Intra-aortic balloon assistance was, therefore, of most value in patients dependent on cardiopulmonary bypass. The survival in patients with cardiogenic shock after myocardial infarction was marginally improved.

The principle of intra-aortic balloon counterpulsation was first suggested by Moulopoulos *et al.* (1962), and it was subsequently developed for use in cardiogenic shock after myocardial infarction. A balloon catheter positioned at the top of the descending aorta is inflated in diastole and augments the aortic diastolic pressure, thus increasing coronary artery perfusion. With balloon deflation before the beginning of ventricular systole, left ventricular afterload is reduced, with a consequent reduction in ventricular oxygen consumption. A number of patients with cardiogenic shock have now been treated in this way (Kantrowitz *et al.*, 1968b; Dunkman *et al.*, 1972; Scheidt *et al.*, 1973; O'Rourke *et al.*, 1975). Hospital survival may be improved using this technique but authors have varied in the criteria used for concomitant corrective surgery (Mundth *et al.*, 1971; Leinbach *et al.*, 1973; Windsor *et al.*, 1973). Following its use for patients in cardiogenic shock after myocardial infarction intra-aortic balloon assistance has been used in patients with advanced cardiovascular failure after cardiopulmonary bypass (Berger *et al.*, 1973; Buckley *et al.*, 1973a; Housman *et al.*, 1973; Parker *et al.*, 1974). This paper presents our experience over 24 months with the technique in the treatment of cardiac surgical patients and patients in cardiogenic shock after myocardial infarction.

Patients

Sixty-eight patients were referred, of whom 55 were accepted for intra-aortic balloon assistance: 31 patients in cardiogenic shock after myocardial infarction and 24 cardiac surgical patients. Of the accepted patients 23 were referred from units outside our own, 16 postinfarction and 7 surgical patients.

CARDIAC SURGICAL PATIENTS

Of the 24 cardiac surgical patients, 15 had the balloon catheter inserted in theatre and intra-aortic balloon counterpulsation started there; 10 of these patients were treated in our own unit and the remainder in outside units. These were all patients who could not be weaned from total cardiopulmonary bypass despite a left ventricular vent with total supportive bypass, and maximal

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catecholamine support which was used in at least two attempts to dispense with cardiopulmonary bypass. The patients remained on full supportive bypass while the balloon catheter was inserted. The mean time elapsed between the first attempt to dispense with cardiopulmonary bypass and the initiation of intra-aortic balloon pulsation in the patients treated in our own unit was 65 minutes (range 20 to 85 minutes). The equivalent time in patients treated in the units outside our own was largely dependent upon transportation time and was, therefore, considerably longer. These 15 patients had had a variety of surgical procedures undertaken; there were 9 single valve replacements (5 aortic and 4 mitral valves), 2 double valve replacements and 4 patients who had had coronary artery bypass grafts with the additional resection of a left ventricular aneurysm in 2 patients.

Nine patients were treated for cardiogenic shock in the acute postoperative phase. Five of these patients had undergone coronary artery surgery and had received two or more bypass grafts. One patient was treated after aortic valve replacement, two after double valve replacements, and one after mitral valve replacement with the additional closure of a secundum atrial septal defect. The balloon catheter in these acute postoperative patients was inserted at the bedside in the intensive care unit of the referring hospital.

MYOCARDIAL INFARCTION PATIENTS

The patients in cardiogenic shock after myocardial infarction all had evidence of an acute infarct on the electrocardiogram. The other criteria for acceptance were:

(1) A peak systolic arterial pressure of less than 90 mmHg confirmed by arterial cannulation.

(2) A urine flow of less than 20 ml per hour, measured by bladder catheterisation, in spite of diuretic challenge.

(3) Either mental clouding or a significant degree of peripheral skin cooling.

All of the above features had to be present for at least two hours before a patient was accepted on clinical criteria as having cardiogenic shock. They had all received conventional medical treatment which proved ineffective before intra-aortic balloon assistance. The policy was to exclude patients in whom potentially treatable factors could be identified; thus they were excluded if the pulmonary wedge pressure was less than 18 mmHg, indicating potentially reversible hypovolaemia, or if the cardiogenic shock was thought to be the result of a reversible cardiac arrhythmia. In practice none of the patients referred to us had either of these problems. Following confirmation of the acceptance criteria the balloon catheter was inserted under local anaesthetic at the bedside in the coronary care unit of the referring hospital and balloon assistance was started there. Patients treated in peripheral hospitals who required further investigation with a view to operation were transported in an ordinary ambulance on continuing balloon assistance to enable these investigations to be performed.

Methods

A Datascope System 80 was used with a Datascope unidirectional catheter (Bregman and Goetz, 1971; Bregman *et al.*, 1971). A 35 ml balloon was used in the majority of patients though a 30 ml balloon was available for smaller patients. The catheters were all inserted by femoral artery cutdown through an end-to-side 'dacron' graft (Kantrowitz *et al.*, 1968a). The position of the catheter was cofirmed by subsequent chest *x*-ray examination. The recording of arterial pressure from a radial artery cannula and of the electrocardiogram taken from praecordial electrodes, are both essential for the timing of balloon inflation and deflation. When necessary an endocardial pacing system was used. In the cardiac surgical patients any further monitoring was based on the practice of the referring unit. Pulmonary artery wedge pressure was determined in the postinfarction group using Swann Ganz flow-directed catheters. The patients in the postinfarction group were routinely anticoagulated with heparin intravenously in a dose of 1000 units hourly. Anticoagulation was not usually used in the surgical groups until 48 hours after operation. All the patients in cardiogenic shock after myocardial infarction had been receiving catecholamine support before intra-aortic balloon assistance was started. Though this was continued during the first few hours of balloon assistance, the intention was always to dispense with all pharmacological support before any reduction in mechanical support. After 12 to 24 hours the patients' dependence was assessed by temporary withdrawal of balloon assistance. Deterioration in mean arterial pressure, a rise in pulmonary artery wedge pressure, or the recurrence of ischaemic pain were taken as indicators of dependence. No patient was judged to be balloon independent while still on a catecholamine infusion.

Results

The influence of intra-aortic balloon counterpulsation in a patient in cardiogenic shock after cardiac surgery is illustrated in Fig. 1. The augmentation of diastolic pressure and the reduction of systolic pressure during support with the balloon are immediately apparent.

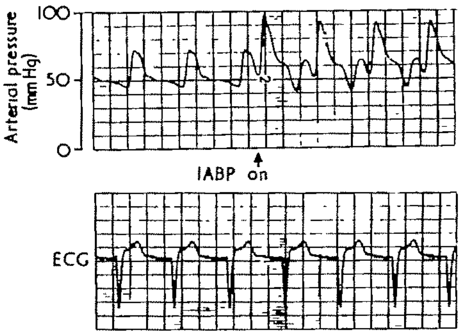

Fig. 1 *A radial artery pressure tracing and electrocardiogram taken from a patient in cardiogenic shock after cardiac surgery. As the balloon pump is switched on there is an immediate augmentation of early diastolic pressure from 53 to 97 mmHg and peak systolic pressure is reduced from 72 to 64 mmHg.*

INTRA-AORTIC BALLOON ASSISTANCE AFTER CARDIAC SURGERY

Of the 15 patients who were totally dependent on cardiopulmonary bypass, 11 could be weaned from it with balloon assistance. Five of these patients survived to leave hospital, having required balloon assistance for a mean period of 24 hours (range 2 to 50 hours). They remained fit and well 6 to 24 months later. This represents a salvage rate of 33 per cent in the bypass dependent group who would otherwise have died in theatre. During the period of study, 277 patients were submitted to open heart surgery in King's College Hospital, and 10 (4%) required balloon assistance as they were bypass dependent. Four of these patients had had mitral valve replacements, 3 had had aortic valve replacements, and of the remaining 3, one had an aortic valve replacement with a coronary artery bypass graft, one a double valve replacement and in the remaining patient a left ventricular aneurysm was resected. Of these 10 patients 8 (80%) could be weaned from bypass using intra-aortic balloon assistance and 4 (40%) were hospital survivors.

Intra-aortic balloon assistance produced haemodynamic improvements in only 5 of the 9 patients treated later in the postoperative period. Four of these survived to become balloon independent but only one of them survived to leave hospital. These patients were assisted for a mean period of 42 hours (range 5 to 12 hours).

CARDIOGENIC SHOCK AFTER MYOCARDIAL INFARCTION

Of the 44 patients referred, 31 were finally accepted for balloon assistance, 15 from our own unit and 16 from outside units. Patients without definite electrocardiographic evidence of myocardial infarction were not accepted, and in practice this involved the exclusion of 2 patients who were subsequently shown to have suffered dissection of the aorta. Secondly, patients over the age of 65 were not accepted and this was the major cause for refusal. Finally there were 2 patients who could not be accepted for treatment as the apparatus was in use elsewhere. Balloon catheter insertion failed in 2 of the 31 accepted patients, because of the presence of iliofemoral atheroma. Both of these patients subsequently died within hours. A further 6 patients died before intra-aortic balloon assistance could be established; all of them had sustained a cardiac arrest before the insertion procedure had started. There were, therefore, 23 patients in whom the surgical procedure involved in inserting the catheter was completed and intra-aortic balloon assistance established.

The control data of the 23 patients established on balloon pulsation are shown in Fig. 2. Only 2 patients were assisted who had been in cardiogenic shock for longer than 12 hours, both of them subsequently died on continued assistance. In the remainder of the patients the mean delay between the onset of cardiogenic shock and the establishment of balloon assistance was 7 hours (with a range of 2 to 12 hours). The time elapsing between the onset of symptoms of myocardial infarction and the diagnosis of cardiogenic shock was variable. Two main groups are apparent; first, 16 patients who developed cardiogenic shock within 24 hours of the first pain of myocardial infarction (mean time 13, range 3 to 22 hours). Secondly, 7 patients who

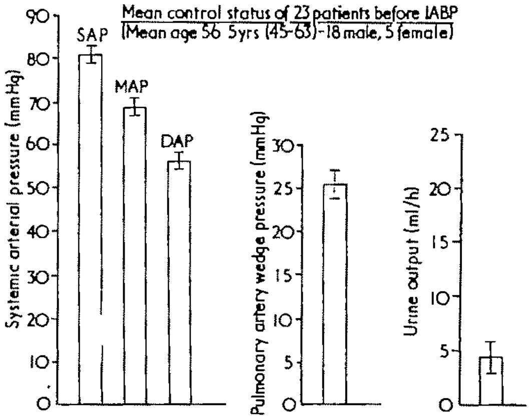

Fig. 2 *The control mean systemic arterial pressures, mean pulmonary artery wedge pressure, and urine output during the preceding hour of the 23 patients established on intra-aortic balloon assistance after myocardial infarction.*

developed shock from 1 to 7 days after their initial symptoms. Fourteen of the patients had electrocardiographic evidence of anterior wall infarction, 6 of inferior wall infarction, and there were 3 patients who had evidence of new changes in both anterior and inferior leads. Eleven patients had had a previous mycardial infarction. One patient had an acquired ventricular septal defect which was confirmed at subsequent cardiac catheterisation. Acute mitral regurgitation was not responsible for shock in any patient.

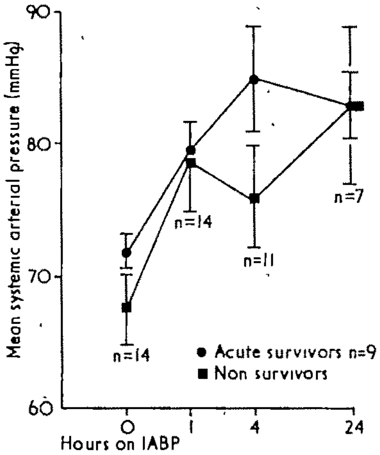

Fig. 3 *The response of mean arterial pressure to intra-aortic balloon assistance in patients with cardiogenic shock after myocardial infarction.*

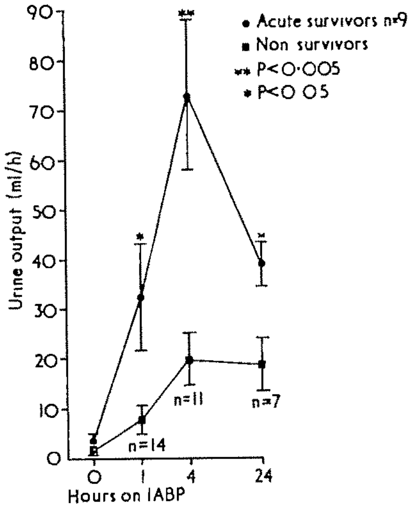

Fig. 4 *The response of urine flow to intra-aortic balloon assistance in patients with cardiogenic shock after myocardial infarction.*

The response of mean arterial pressure in the first 24 hours of assistance is shown in Fig. 3. The patients are divided into two groups. First, 9 patients who survived the acute phase of cardiogenic shock and who then either had the balloon catheter removed (7 patients), or who being haemodynamically stable, but balloon dependent, were submitted to corrective surgery. Secondly, those 14 patients who failed to survive the acute phase, of whom half died during the course of the first 24 hours. There was no significant difference in the response of mean arterial pressure between these two groups of patients. However, the response of urine output to balloon assistance provided a reliable prognostic indicator. Fig. 4 shows the urine flow in the same two groups of patients at the same time. There was a uniform and copious increase in the urine output of the acute survivors which is significantly greater than that of the non-survivors at 1, 4, and 24 hours. The non-survivors also showed an increase in urine output at these times which was significantly greater than the control value ($P < 0{\cdot}01$).

Diagnostic cardiac catheterisation, including coronary angiography and left ventriculography, was performed in 10 patients. During the first year of the experience presented here, coronary angiography was performed only on those patients who were haemodynamically stable but balloon dependent. In the latter part of the experience, however, all patients who achieved haemodynamic stability were investigated. Emergency revascularisation was only considered in the balloon-dependent group. Of these 8 balloon-dependent patients, only one had an adequate run-off visible on the coronary arteriogram distal to a proximal stenosis and proceeded to surgery. This patient had been haemodynamically stable for 48 hours and underwent coronary artery bypass grafting to two arteries. One further patient with a large anterior septal myocardial infarction developed a ventricular septal defect giving rise to a 3 : 1 left-to-right shunt. After a period of intra-aortic balloon assistance he was submitted to operation 7 days after the onset of symptoms. Neither of the 2 patients who were operated upon could subsequently be weaned from cardiopulmonary bypass.

Of the 23 established patients, therefore, 5 survived to leave hospital. Three of them are alive 6 to 24 months later. This represents a hospital survival of 23 per cent in the patients established on intra-aortic balloon assistance. Acute survivors required balloon assistance for a mean 30 hours (range 19 to 70 hours). The non-survivors died after 2 to 32 hours of assistance.

COMPLICATIONS

The only complications encountered were the result of the reduction of arterial flow in the iliofemoral system through which the balloon catheter was inserted. Five patients had evidence of impaired circulation. Two of these failed to show any significant haemodynamic response and both died before impairment of peripheral circulation required any action. One patient had been judged to be balloon independent after myocardial infarction, and the balloon catheter was removed from the affected leg earlier than would otherwise have been intended. Though satisfactory recirculation to the leg was established in this patient, he subsequently suffered further haemodynamic deterioration and died. There were two patients in the surgical group, one of whom had been cardiopulmonary bypass dependent in theatre in another hospital. They both became haemodynamically stable after intra-aortic balloon assistance but required limited amputation (one below knee and one above knee) because of lower limb ischaemia after removal of the balloon catheter. Both of these patients died later in their hospital course. In one death was the result of incidental biliary peritonitis resulting from a rupture of the gall bladder, and in the other an acute myocardial infarction developed because of thrombotic occlusion of the bypass graft. In one further patient there was necropsy evidence that the balloon catheter had caused a limited aortic dissection through an atheromatous plaque at the iliofemoral junction subsequently re-entering the aortic lumen, with no clinical evidence of arterial impairment. There were no embolic complications in any of the patients in this series. The insertion of the balloon catheter with subsequent balloon assistance was not thought to have caused death in any patient.

Discussion

Intra-aortic balloon counterpulsation has two major haemodynamic effects. Inflation of the balloon at the start of diastole produces augmentation of the aortic diastolic pressure. In the conditions that obtain in cardiogenic shock, autoregulation probably has little part to play in the control of coronary blood flow (Mueller *et al.*, 1973), leaving coronary artery filling pressure as the major determinant of flow (Powell *et al.*, 1970). Thus Mueller *et al.* (1971) found that coronary artery flow increased in patients over the first 4 to 6 hours of balloon pumping. However, in patients who had recovered from the acute phase of cardiogenic shock as a result of treatment with intra-aortic balloon assistance and who were investigated 17 hours after the initiation of therapy, Leinbach *et al.* (1971) were unable to show any significant effect on coronary artery flow. This finding may represent recovery of autoregulatory function in the coronary arteries with haemodynamic improvement. The second haemodynamic effect of intra-aortic balloon assistance results from deflation of the balloon before the onset of ventricular systole, which produces a forward flow in the column of blood between the aortic valve and the balloon at the top of the descending aorta. This results in a lowering of peak systolic pressure generated by the left ventricle which in turn has a favourable effect on myocardial oxygen consumption (Soroff *et al.*, 1963; Mueller *et al.*, 1971).

Cardiogenic shock occurring in the acute phase of myocardial infarction is universally accepted to carry a poor prognosis. However, the exact hospital mortality is variously quoted and depends upon the diagnostic criteria used. Scheidt *et al.* (1970) found a hospital mortality of 86 per cent in patients managed medically. Scheidt *et al.* (1973) later emphasised that the mortality in shocked patients refractory to conventional medical treatment increases and probably approaches 100 per cent. All the patients in the present study were refractory to conventional medical therapy.

The criteria used for the acceptance of patients after myocardial infarction in this study were of necessity purely clinical as it was our aim to provide a service in coronary care units which do not necessarily have the facilities for detailed haemodynamic investigation. Furthermore, O'Rourke *et al.* (1975) emphasised 'the relentless deterioration' occasioned by prolonged haemodynamic assessment. Though the criteria which were applied appear to have successfully identified a critically ill group of patients, in common with other reviews of experience with intra-aortic balloon assistance in cardiogenic shock, there is no satisfactory control group. It is, therefore, difficult to be certain of the true extent to which intra-aortic balloon assistance improves survival in the present study. In a search for suitable controls, the two patients in whom balloon catheter insertion failed and subsequently died would not be representative by virtue of the advanced state of disease in their peripheral arteries. Similarly, those whose age precluded consideration of intra-aortic balloon assistance are also unrepresentative. A more suitable control group would be provided by those patients who fulfilled the acceptance criteria, but could not be offered intra-aortic balloon assistance because the apparatus was in use elsewhere. To date, however, there have been only two such patients, both of whom died.

The overall hospital survival in patients established on intra-aortic balloon assistance with shock after myocardial infarction which was refractory to conventional medical therapy was 22 per cent of the present series. This compares favourably with 17 per cent of 87 reported by Scheidt *et al.* (1973), 16 per cent of 44 patients reported by Dunkman *et al.* (1972), 24 per cent of 80 patients reported by Leinbach *et al.* (1973), and 11 per cent of the 18 patients reported by Willerson *et al.* (1975). It is less favourable than the 35 per cent achieved in patients in shock by O'Rourke *et al.* (1975). Clearly one of the problems is to identify the appropriate place of angiography and corrective surgery. The role of intra-aortic balloon assistance in the management of acquired ventricular septal defects and acute mitral regurgitation has been described and recently emphasised (Buckley *et al.*, 1973b; Slama *et al.*, 1975). Though the only such patient reported here subsequently died at operation, he was at least operated upon while well perfused and polyuric, having been anuric and in a state of profound cardiogenic shock 48 hours previously in a peripheral hospital. We now regard the presumed presence of an acquired ventricular septal defect associated with anything more than mild haemodynamic impairment as a positive indication for intra-aortic balloon assistance after myocardial infarction (Slama *et al.*, 1975). The role of emergency revascularisation with or without infarctectomy is more problematical. It seems reasonable to confine attempts at emergency revascularisation to the group of patients who are haemodynamically stable but balloon dependent (Leinbach *et al.*, 1972, 1973). In the series reported here, however, there were few patients who were balloon dependent and who survived for a significant period of time. It is for this reason that few attempts at emergency revascularisation were made. The question remains as to whether the balloon independent group should be submitted to coronary angiography. On the one hand is the obvious reluctance to submit this group of patients to any further risk. On the other hand there is a disquieting situation which occurred in 2 patients who became balloon independent but who deteriorated and died later in their hospital course after removal of the balloon catheter. Had an assessment of their operability been available as a result of prior angiography, a decision to reinstitute intra-aortic balloon assistance and perhaps undertake late surgery would have been reached more easily.

Despite the difficulty, referred to above, in assessing the benefit of this treatment in the absence of control patients, there appears to have been an increased survival in the shocked group of patients after myocardial infarction shown here which, albeit marginal, certainly justifies the continued use of intra-aortic balloon assistance in cardiogenic shock. However, this is a relatively rare condition. Kuhn (1974) found only 28 shocked patients in 636 consecutive cases of myocardial infarction, only 10 (1·5%) of whom were aged less than 65. Most of these patients will, of course, present to district hospitals and it is there that the attempt to salvage them must be made. We have shown that intra-aortic balloon assistance can be satisfactorily provided on a regional basis using no more specialised equipment than the system itself. Presentation to a peripheral hospital did not affect the mortality adversely but rather the reverse, since all our survivals after myocardial infarction initially came from outside our own unit.

It is particularly pertinent to consider what role intra-aortic balloon assistance might have in the management of patients whose cardiovascular failure occurs after infarction but in whom deterioration and the development of frank cardiogenic shock have not yet occurred. Since even in cardiogenic shock haemodynamic improvement occurred in 19 of the 23 patients established on intra-aortic balloon assistance it is attractive to consider using it in a less severe group. The hope would be that the augmentation of coronary blood flow, together with the reduction of left ventricular afterload and therefore myocardial oxygen consumption, would reduce or limit infarct size and so improve mortality. The difficulties of designing a suitably controlled prospective trial of this invasive therapy in less-sick patients has to date limited its application. It is likely that in the future such an application will be more extensively studied.

In the management of cardiac surgical patients there was a clear distinction in the efficacy of intra-aortic balloon assistance between the two categories; those who were totally dependent on cardiopulmonary bypass and treated in theatre, and those who were treated later in the intensive care unit. In the second group 3 patients were treated in the first few months of our experience and a further 3 in units outside our own. Treatment may, therefore, have been unduly delayed. Nevertheless, the failure of 4 of the 9 patients to show any haemodynamic response to intra-aortic balloon assistance and the hospital survival of only one cannot be considered encouraging. In contrast there were 15 patients who were cardiopulmonary bypass dependent and presumably without intra-aortic balloon assistance they would all have died. The fact that 10 were subsequently weaned from cardiopulmonary bypass and 5 (33%) survived to leave hospital shows the effectiveness of intra-aortic balloon assistance in this category of patients. The balloon pump, therefore, finds its major application in the resuscitation of patients totally dependent on cardiopulmonary bypass and it must be considered an essential adjunct to the practice of cardiac surgery.

We are grateful to the physicians and cardiac surgeons who referred patients in advanced cardiovascular failure to us.

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Mechanisms of angina relief in patients after coronary artery bypass surgery[1]

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The mechanisms underlying the relief of angina after coronary bypass surgery have been studied by analysing the results of the baseline and follow-up treadmill tests on patients included in a prospective randomised study of surgical versus medical treatment of stable angina pectoris. There were 22 surgically treated patients and 35 medically treated patients, whose endpoint on the initial treadmill tests was angina with concomitant ischaemic ST depression. At one year, 91 per cent of the surgically treated patients had no chest pain during the exercise test while only 11 per cent of the medically treated patients were free from angina ($P<0{\cdot}001$). Exercise tolerance was significantly better in both groups but improvement was greater in the surgically treated patients (exercise tolerance increased by 98% compared with 28%). The product of heart rate and systolic blood pressure measured at the maximal exercise level was also increased significantly in the surgically treated patients, whereas this product decreased slightly in the medically treated patients. Of the surgically treated patients, 59 per cent had ischaemic ST depression on the exercise electrocardiogram but did not develop anginal pain, compared with only 9 per cent of the medically treated patients ($P<0{\cdot}001$). These data suggest that in addition to increased coronary blood flow, for which the increased product of heart rate and blood pressure is indirect evidence, trauma to nerves and possibly other nonspecific factors related to surgery may be important mechanisms contributing to the relief of angina after coronary bypass surgery.

The surgical treatment of ischaemic heart disease using the saphenous vein bypass technique has become widely accepted. This procedure has resulted in excellent symptomatic results with complete relief of, or considerable improvement in angina in a high percentage of patients (Favaloro, 1972; Reul *et al.*, 1972; Hall *et al.*, 1973; Segal *et al.*, 1973; Najmi *et al.*, 1974; Mathur and Guinn, 1975; Ross, 1975). The preliminary results of a randomised study performed in our hospital (Mathur and Guinn, 1975) clearly showed that angina was improved and the quality of life better in the operated patients compared with the medically treated patients.

Despite extensive use of this surgical procedure, a major question that remains unanswered concerns the mechanisms responsible for the symptomatic improvement. It is believed that restoration of adequate coronary blood flow with consequent improvement in oxygen delivery to the ischaemic myocardium is the main factor underlying pain relief after coronary artery bypass. However, significant improvement or complete relief of angina has been noted in some patients with occluded grafts (Griffith *et al.*, 1973a; Di Luzio *et al.*, 1974; Campeau *et al.*, 1976). Also, many surgically treated patients have been found to develop ischaemic ST depression on follow-up treadmill testing, but without chest pain (Bartel *et al.*, 1973; Berndt *et al.*, 1975). These observations raised the question whether the increased oxygen delivery was the sole mechanism underlying the improvement of angina, and attempts have been made to identify other contributory factors. These include: (1) infarction of ischaemic myocardium during operation (Hultgren *et al.*, 1971; Brewer *et al.*, 1973; Griffith *et al.*, 1973b; Di Luzio *et al.*, 1974; Ross, 1975), (2) possible improvement of left ventricular function (Chatterjee *et al.*, 1972; Hammermeister *et al.*, 1974), (3) denervation of ischaemic areas (Soloff, 1973; Ross, 1975), and (4) the placebo effect of surgery (Cobb *et al.*, 1959; Dimond *et al.*, 1960; Spodick, 1971; Campeau *et al.*, 1976).

The purpose of this report is to elucidate this problem further by analysing the results of treadmill exercise testing in two similar groups of

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patients with angina, selected randomly for surgical or medical treatment.

Patients and methods

The treadmill exercise data of the patients included in a prospective randomised study of surgical versus medical treatment of stable angina pectoris (Mathur and Guinn, 1975) were reviewed. Since the object of this study was to evaluate the mechanisms underlying the relief of chest pain after operation, the subjects were selected for inclusion in this analysis if they satisfied the following criteria: (1) availability of an adequate prerandomisation treadmill test where the endpoint was definite angina with accompanying ischaemic ST depression, (2) availability of a follow-up treadmill test at 1 year or more after randomisation.

The treadmill tests were performed according to the Bruce protocol (Bruce and Hornsten, 1969). Two modified bipolar transthoracic electrocardiographic leads were monitored, using the V5 and V6 positions. Resting records of these two leads were obtained both in the sitting and standing positions before starting the exercise test. Records were then obtained at 1-minute intervals during exercise, at the end of the exercise period, and subsequently at 3-minute intervals until return to baseline. The blood pressure was determined using a standard clinical sphygmomanometer every 3 minutes, before increasing the exercise load from one stage to the next. The patients were exercised to symptomatic endpoints: moderately severe angina, dyspnoea, or exhaustion.

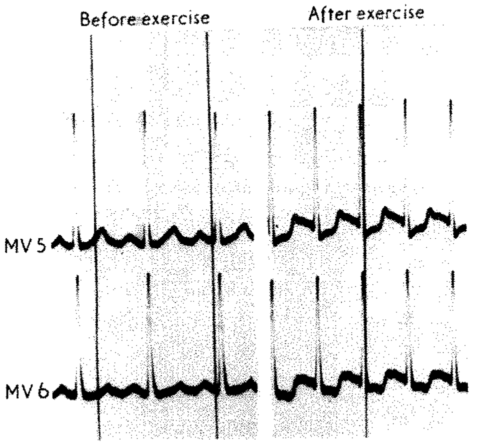

Fig. 1 *An example of the treadmill test: electrocardiograms (bipolar transthoracic leads in V5 and V6 positions) recorded from one of the surgical patients who stopped because of fatigue. Note the exercise-induced ischaemic ST segment depression.*

A treadmill test was interpreted as positive for ischaemia if the exercise resulted in 1 mm or more of horizontal or downsloping ST segment lasting 0·08 s or more, in the absence of digitalis, diuretics, or other drugs known to produce false positive tests (Fig. 1). A test was considered negative if no significant ST segment changes occurred though the patient attained 85 per cent or more of his predicted maximal heart rate. It was considered inconclusive if the patient had no significant ST changes but failed to attain 85 per cent of predicted maximal heart rate or if ST changes occurred but the patient was receiving digitalis or other drugs known to produce such ST changes.

All patients who were included in the prospective randomised study underwent cardiac catheterisation and coronary angiography before randomisation. The presence of critical coronary arterial stenosis (70% or more decrease in lumen diameter) in one or more major vessels was a prerequisite for inclusion in the study. Catheterisation and angiography were repeated about 1 year after randomisation on all patients in both treatment groups. Informed consent was obtained for all the studies performed. The statistical analysis was performed using the Student's t test and χ^2 test.

Results

There were 57 patients, allocated randomly to surgical or medical treatment, who satisfied our selection criteria (availability of a prerandomisation positive treadmill with angina as the endpoint and availability of follow-up treadmill at one year or more). Twenty-two patients had had a coronary bypass operation and of these 20 (91%) had no chest pain during the 1-year follow-up treadmill test, while of the 35 who were randomised to the medical treatment group only 4 (11%) had no chest pain during the treadmill test performed at one year ($P < 0{\cdot}001$).

The treadmill data of the surgical patients are summarised in Table 1 and those of the medical patients in Table 2. Comparison of the baseline data of the surgical and medical patients showed no significant difference in duration of exercise, maximal heart rate attained, maximal systolic pressure, or maximal product of heart rate × systolic pressure (the double product). Fig. 2 shows a schematic display of the exercise tolerance time and the double product observed in the surgical and medical groups. Both surgically and medically treated patients significantly improved their exercise tolerance at 1 year, though the

Table 1 *Surgical group*

	Baseline	*One year*	*% Change*	*P*
Duration of exercise	3 min 48 s	7 min 32 s	+98	<0·001
Maximal heart rate	134 ±6	150 ±5	+12	<0·01
Maximal systolic blood pressure	150 ±5	177 ±8	+18	<0·01
Maximal double product	20112 ±1293	26922 ±1803	+34	<0·01

Table 2 *Medical group*

	Baseline	*One year*	*% Change*	*P*
Duration of exercise	3 min 57 s	5 min 5 s	+28	<0·001
Maximal heart rate	138 ±3	126 ±3	− 9	<0·01
Maximal systolic blood pressure	148 ±4	145 ±3	− 2	NS
Maximal double product	20960 ±787	18469 ±608	−12	<0·01

Table 3 *Results of treadmill test at 1 year*

	Medical treatment	*Surgery*	*P*
Ischaemic ST depression and angina	28 (80%)	2 (9%)	<0·001
Ischaemic ST depression, no angina	3 (9%)	13 (59%)	<0·001
Negative treadmill test	0 (0%)	6 (27%)	<0·05
Inconclusive	4 (11%)	1 (5%)	NS
	35	22	

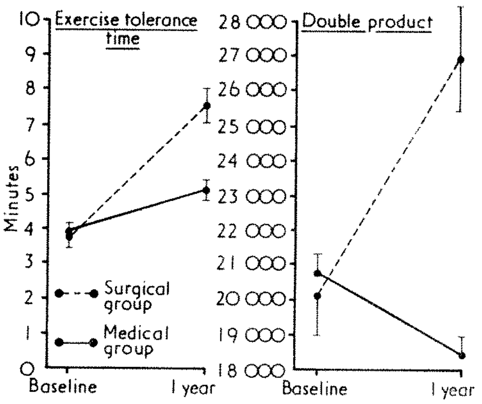

Fig. 2 *Effect of surgical versus medical management on the exercise tolerance and the maximal double product (systolic blood pressure × heart rate). Note that there was no significant difference between the base-line values. Exercise tolerance improved significantly in both groups but more so in the surgical group. The double product increased significantly in the surgical group but decreased in the medical group.*

surgical patients clearly performed better than the medical patients. The double product also increased significantly in the surgical patients, while in the medical patients it decreased slightly.

Further analysis of the treadmill data obtained at 1 year, relating the presence or absence of chest pain to the presence or absence of ischaemic ST segment changes on the monitored electrocardiographic leads, is summarised in Table 3 and displayed schematically in Fig. 3. At 1 year, 13 surgical patients (59%) had ischaemic ST depression without angina, while this occurred in only 3 (9%) of the medically treated patients ($P < 0{\cdot}001$). The overwhelming majority of the medical patients (80%) had ST depression and angina.

In an attempt to find a possible explanation for this higher incidence in the surgical group of ischaemic ST depression without angina on the treadmill test, the following factors were carefully reviewed in the 13 patients with this finding: (1) presence of perioperative myocardial infarction: only 1 (8%) had a definite perioperative infarct diagnosed on the basis of the appearance of new pathological Q waves on the electrocardiogram; (2) myocardial function, as determined by left ventriculography: there was no significant difference from baseline at 1 year (ejection fraction 64% ± at one year compared to 66% ±4 at baseline); (3) patency of grafts: of the 25 grafts, 22 (88%) were patent upon restudy at 1 year; (4) duration of exercise was increased by 125 per cent from baseline (7′ 58″ vs. 3′ 33″; $P < 0{\cdot}01$); (5 maximum double product was increased by 33 per cent from baseline (27 830 vs. 20 920; $P < 0{\cdot}01$).

In the search for further factors responsible for the improvement of angina, other than the increase of blood flow to ischaemic areas, we also reviewed

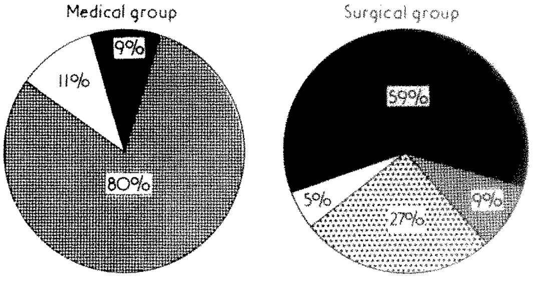

Fig. 3 *Schematic presentation of the treadmill results at one year in the surgical and medical groups.*

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Table 4 *Analysis of 7 surgical patients with all grafts occluded*

	Baseline	*One year*	*% Change*
Duration of exercise	4 min 15 s	7 min 37 s	+80
Maximal heart rate	155	161	+4
Maximal systolic blood pressure	159	160	
Maximal double product	23940	25890	+9

all the surgical patients included in the randomised study, searching for cases with occlusion of all grafts. We found 7 such patients, none of whom was included in the present series because they did not satisfy the selection criteria. The treadmill data are summarised in Table 4. Despite the fact that these patients had all their grafts occluded, their exercise tolerance also improved, averaging 80 per cent increase from baseline, and 4 of the 7 had no angina upon treadmill testing at 1 year. There was no statistically significant increase in their maximal double product.

Discussion

Comparing the results of surgical and medical management, as assessed by treadmill testing at 1 year after starting treatment, it is apparent that the surgically treated patients were able to exercise longer with significantly lower incidence of chest pain than the medically treated patients. These results compare well with others' observations of significant improvement of exercise performance after bypass surgery (Mason *et al.*, 1971; Bergman *et al.*, 1971; Bartel *et al.*, 1973; Lapin *et al.*, 1973; Aronow and Stemmer, 1974; Knoebel *et al.*, 1974; Merrill *et al.*, 1975). It is reasonable to attribute the high incidence of pain relief after surgery to increased oxygen delivery to the ischaemic myocardium through restoration of coronary blood flow. This contention is supported indirectly by the significant increase in the maximum double product (34% increase) and the high percentage of patent bypass grafts, with reasonably good filling of the distal vessels, 1 year after randomisation.

However, a large proportion of the surgically treated patients (13/22) showed ischaemic changes on the electrocardiogram during the treadmill test without developing angina. This observation has also been made by others (Bartel *et al.*, 1973; Berndt *et al.*, 1975) and suggests that there may be additional mechanisms of pain relief after coronary arterial bypass grafting. Several authors (Hultgren *et al.*, 1971; Brewer *et al.*, 1973; Griffith *et al.*, 1973b; Di Luzio *et al.*, 1974; Ross, 1975) have considered the role of non-fatal myocardial infarction in the symptomatic relief of patients by eliminating or reducing the ischaemic focus. However, this factor could not account for the relief of angina in our patients since only one out of 13 had evidence of perioperative myocardial infarction. Another possible explanation is that the perivascular nerves accompanying the coronary arteries are divided or traumatised during the procedure (Soloff, 1973; Ross, 1975). This interruption of the pain pathway from the heart might increase exercise tolerance, and account for the ischaemic ST segment response to the exercise test without angina. Our data favour this possibility since, in the comparable group of medically treated patients where no trauma to nerves can be postulated, only 3 (9%) showed ischaemic ST depression without angina and the difference between the medical and surgical groups was statistically significant in this respect ($P < 0{\cdot}001$). This mechanism appears more likely than a pure placebo effect, since a placebo effect may also be produced by medical treatment. The additional observation that 7 patients all of whose grafts were occluded significantly increased their exercise tolerance, and that 4 of these patients had no angina on the treadmill test performed at one year, also supports the view that trauma to nerves and perhaps a nonspecific placebo effect of surgery may be important factors in the relief of angina.

It is, therefore, concluded that there is more than one mechanism involved in the relief of angina after coronary arterial bypass. Our data suggest that in addition to increased coronary blood flow, trauma to nerves and possibly other non-specific factors related to surgery may be important contributing mechanisms.

We gratefully acknowledge Drs. Henry McIntosh, Gene Guinn, Virendra Mathur, Robert Luchi, Mahir Awdeh, Alfredo Montero, and Tetsuo Ishimori for advice, suggestions, and help in carrying out this study, and Dr. John Thornby for the statistical analysis.

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Persistent ductus arteriosus: most probably a primary congenital malformation

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This study was undertaken in an attempt to determine whether there is a distinct histological difference between the human normally closing ductus arteriosus and a persistent ductus arteriosus. The microscopical investigation was done in 42 specimens of human ductus arteriosus from subjects ranging in age from 12 hours after premature delivery to 32 years. The ducts derived from hearts with various congenital malformations, in some of which patency of the ductus was essential for survival, as well as from hearts without other congenital malformations. Because no histological differences were found between the isolated patent ductus arteriosus and those associated with other congenital heart anomalies, the specimens were classified according to age. Stages of a normal anatomical closing process were not encountered in patients over 4 months of age with a patent duct. Younger material showed either a histologically normal stage of anatomical closure or an abnormality of the ductus wall. This abnormal histology is mainly characterised by an aberrant distribution of elastic material, the most conspicuous feature being a thick, wavy, unfragmented subendothelial elastic lamina. In respect of the question as to whether the observed histological abnormality forms part of a primary anomaly of the ductus arteriosus or is secondary to the prolonged patency, it appears that most of the evidence provides support for the view that a primary anatomical defect of the ductus wall is responsible for persistence of the ductus arteriosus.

The human ductus arteriosus has been the subject of many studies, but most of these investigations concerned normal anatomical closure (e.g. Jager and Wollenman, 1942; Danesino *et al.*, 1955; Bakker, 1962; Hoffmann, 1964; Desligneres and Larroche, 1970) or physiological closure (e.g. Eldridge and Hultgren, 1955; Adams and Lind, 1957; Rudolph *et al.*, 1961). Many studies have also been based on animal material (e.g. Sciacca and Condorelli, 1960; Hoefsmit, 1967; Hörnblad, 1969; Broccoli and Carinci, 1973). The monograph by Cassels (1973) entitled *The Ductus Arteriosus* provides an abundance of information on the human ductus arteriosus, covering a great many fields of interest and giving a good review of the literature. There is, however, sparse material published on the histology of persistent ductus arteriosus. Some comments are given by Bakker (1962), Desligneres and Larroche (1970), and Cassels *et al.* (1975). With respect to the pathogenesis of the persistent type, Cassels *et al.* (1975) think it reasonable to conclude that in some groups of heart malformations the haemodynamic oxygen tension plays a significant role in the patency of the duct, whereas in others its persistent function as an open vessel is probably a facet of the congenital heart disease complex and related chiefly to an anomaly of the wall. The anomaly could be located at several sites in the ductus. Cassels and Moore (1973) mention that in persistent patency in man there is a deficiency of catecholamines in the duct. In addition, there might be an anomaly of the smooth muscle or oxygen receptors (Cassels *et al.*, 1975).

The question of whether persistent ductus arteriosus might be caused by an underlying abnormality of the ductus wall became especially important after the influence of the prostaglandins and their inhibitors on the closing process of the ductus became known. These drugs might be used in infants with diseases in which either closure or patency of the ductus arteriosus could be lifesaving (Sharpe and Larsson, 1975; Sharpe *et al.*, 1975; Friedman *et al.*, 1976; Heymann *et al.*, 1976; Nadas, 1976; Olley *et al.*, 1976; Moulaert *et al.*, 1977).

The aim of the study reported here was to determine whether there is a pronounced histological difference between the normally closing human ductus arteriosus and a persistent ductus arteriosus.

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Table *Material*

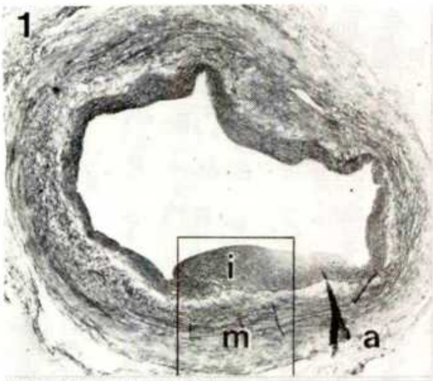
Group	*Case No.*	*Code No.**	*Age*	*Heart anomalies*	*Sex*	*Intima cushions*	*Internal elastic lamina*	*Subendothelial elastic lamina*	*Amount of elastic material*	*Remarks*
I	1	5673	2 d	—	♂	+	+	—	—	Prem. 32 wk
	2	5816	3 d	—	♂	+	+	—	—	Prem. 35 wk
	3	3609	12 h	—	♂	—	+	—	—	Prem. 36 wk (Fig. 5)
II	4		0 h	—	♀	+ +	+	+	—	5407–'61 (Fig. 8)
	5	3786	8 h	T	♂	+	+	—	—	
	6	3630	10 h	T	♂	+	+	—	—	
	7	1080	12 h	P	♂	+	+	—	—	
	8	3966	1 d	L	♀	+	+	—	—	
	9	2602	1 d	T	♂	+	+	—	—	
	10	301	1 d	—	?	+	+	—	—	
	11	4314	2 d	L	♂	+ +	+	—	—	
	12	3057	2 d	L	♂	+ +	+	—	—	(Fig. 1, 2, 3a)
	13	2060	2 d	—	♀	+	+	—	—	2 dissecting aneurysm
	14	3629	3 d	—	♀	+ +	+	—	—	
	15	3967	4 d	L	♀	+ +	+	—	—	
	16	3644	5 d	L	♂	+ +	+	—	—	
	17	3049	6 d	L	♀	+ +	+	—	—	
	18	2782	6 d	T	♂	+ + +	+	—	—	Almost closed (Fig. 3b)
III	19	1901	8 d	T	♀	+ +	+	—	—	
	20	4166	9 d	—	♀	+ + +	+	—	—	
	21	4396	14 d	—	?	+ + +	+	—	—	
	22	2587	17 d	T	♂	+ + +	+	+	+	Fig. 7
	23	5452	1 m	L	♀	+ + +	+	—	—	
	24	5670	1½ m	L	♂	+ +	+	—	—	
	25	2780	1½ m	T	♂	+ + +	+	—	—	Almost closed (Fig. 4)
	26	1538	2 m	L	♂	—	—	—	+ + +	Fig. 6
	27	2648	2 m	L	♀	+	+	+	—	
	28	1405	2 m	—	♂	+ + +	+	—	—	Almost closed
IV	29	3900	4 mth	VSD	♀	+	+	+	—	
	30	1039	4 mth	T	♂	+	+	+	+ +	
	31	2663	4 mth	—	?	—	—	+	+ + +	
	32	15	4½ mth	P	♂	+	+	+	+	
	33	5783	7 mth	VSD	♂	+ +	+	+	—	
	34	2278	8 mth	T	♂	+ +	+	+	—	Fig. 9
	35	792	11 mth	VSD	♀	+ +	+	+	—	
	36	1830	13 mth	P	♂	+	+	+	+ +	Thromb. in trunc. pulm.
	37		2 y	OAVC	♀	+	+	+	+	3104–'61
	38		3 y	OAVC	?	+	+	+	+	10142–'58
	39	2425	4 y	—	?	Pul + +	+	—	—	Almost closed (Fig. 11)
						Ao + +	+	+	—	Patent (Fig. 11)
	40	3645	5 y	—	♀	+	+	+	—	Fig. 10
	41	2642	6 y	—	♀	+	+	+	—	
	42	2574	32 y	—	♂	+	+	+	—	

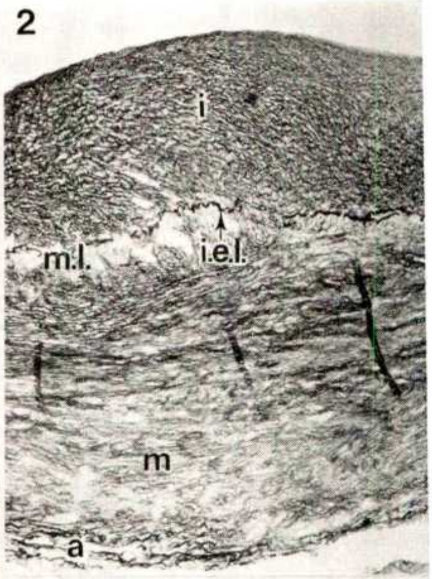
*Code No.: as in the collection of the Laboratory for Anatomy and Embryology, Leiden; T, transposition without ventricular septal defect; P, pulmonary atresia; L, left hypoplastic heart; VSD, ventricular septal defect; OAVC, ostium atrioventriculare commune; —, no other congenital heart anomalies.
Intima cushions: — not present (Fig. 5, 6); + not very distinct (Fig. 10); + + obvious (Fig. 1, 2, 8, 9); + + + very obvious (Fig. 7).
Internal elastic lamina: present +, absent —.
Subendothelial elastic lamina: present +, absent —.
Amount of elastic material: — normal; + slightly more fine fibres (Fig. 7); + + and + + + elastic lamellae present (Fig. 6).
Cases 4, 37, and 38 were kindly put at our disposal by Dr. P. M. Bakker, Leyenburg Hospital, The Hague, and cases 1 and 2 by Dr. A. J. M. G. Moulaert, Wilhelmina Children's Hospital, Utrecht.

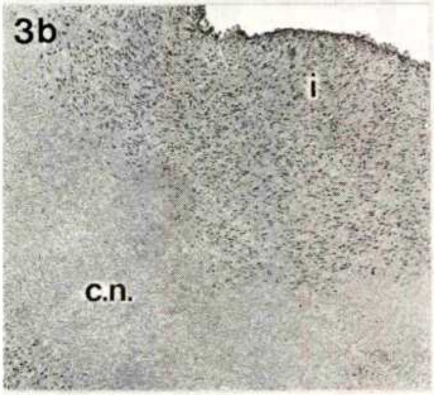
The question of whether any abnormal histological picture found in the wall of a persistent ductus should be considered part of a primary defect or merely a consequence of prolonged patency is also discussed.

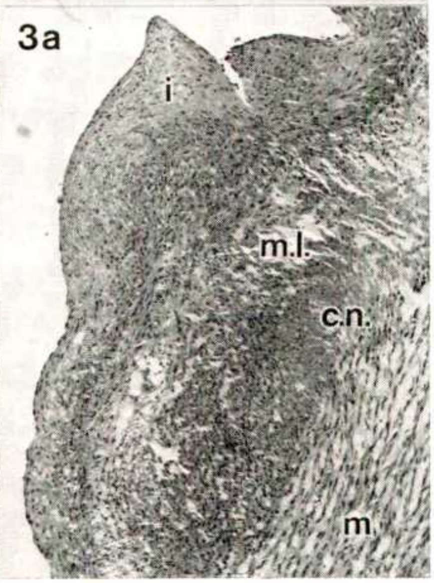
Patients and methods

The material consisted of 42 specimens of human ductus arteriosus from subjects ranging in age from 12 hours after premature delivery to 32 years (Table). These ducts derived from hearts with aortic atresia, pulmonary atresia, transposition without a ventricular septal defect (all anomalies in which patency of the ductus is essential for survival), ventricular septal defect, and ostium atrioventriculare commune, as well as from cases without further congenital heart anomalies. In most of the specimens post-mortem angiocardiography had been performed before anatomical and histological preparation, to show the presence or absence of anatomical patency. According to the published reports (Moss *et al.*, 1963), in full-term infants functional closure normally takes place 10 to 15 hours after birth. Anatomical closure takes much longer, i.e. 1 week to 3 months (Cassels, 1973). On









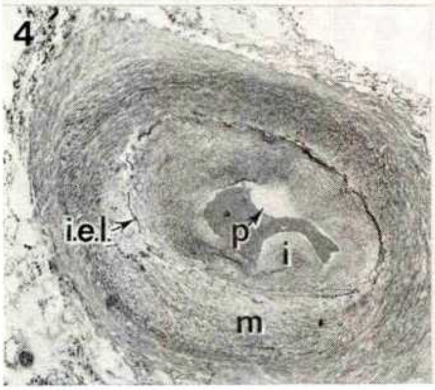


Fig. 1 *Transverse section of a ductus arteriosus showing characteristics of a closing process which started normally. Case 12, aged 2 days. (Weigert elastic stain. ×8.)*

Fig. 2 *Detail of Fig. 1. In the inner third of the media there are mucoid lakes bordering the fragmented internal elastic lamina and the intimal cushions. (×32.)*

Fig. 3 *(a) Detail of the wall of a ductus arteriosus. Mucoid lakes and cytolytic necrosis are present in the inner third of the media. Same case as Fig. 1 and 2 (H. E. ×32.) (b) Detail of a wall showing a large area of cytolytic necrosis. Case 18, aged 6 days. (H. E. ×32.)*

Fig. 4 *Transverse section of an almost closed ductus arteriosus. Postnatal intimal proliferation is completely devoid of elastic material. Case 25, aged 1½ months. (Weigert elastic stain. ×14.)*

Abbreviations used in the figures: a: adventitia; cn: cytolytic necrosis; i: intima cushions; iel: internal elastic lamina; m: media; ml: mucoid lakes; p: postnatal intimal proliferation; sel: subendothelial elastic lamina.

the basis of these data it seems justified to conclude that persistent ductus arteriosus exists at least in all cases where the ductus arteriosus remains patent in infants older than 3 months.

All specimens were sectioned serially and studied microscopically. The plane of section was either longitudinal or transverse. In some cases the ductus was, after cleaving, sectioned in both planes. After sectioning, the material was fixed in alcohol-glycerin for staining with haematoxylin-eosin, azan, Weigert, and van Gieson elastic tissue stains, or resorcin-fuchsin-iron haematoxylin-picric acid-thiazin red (standardised method of Hoefsmit, 1967).

Attention was paid to the characteristics of the normal anatomical closing process of the human ductus arteriosus, which is described by several authors, e.g. Jager and Wollenman (1942), Bakker

(1962), Desligneres and Larroche (1970). We related our findings to the very thoroughly documented study done by Bakker (1962) on the normal closing process. The most characteristic features of the normally closing ductus (Fig. 1–4), which resembles most a muscular artery, are: (1) intimal cushions protruding into the lumen of the ductus; (2) splitting and fragmentation of the underlying internal elastic lamina (Fig. 2); (3) a media containing little elastic material; (4) a large amount of mucoid substance very often concentrated in mucoid lakes, mostly in the inner third of the media. In addition, in the later stages we see the occurrence of (5) cytolytic necrosis (Fig. 3 a, b); and (6) postnatal intimal proliferations on top of the intimal cushions, clearly recognisable by the absence of elastic material (Fig. 4).

The amount and distribution of smooth-muscle cells and fibrous and elastic tissue was also taken into account. The elastic tissue proved to be of great importance for our study.

Results

Since no histological differences could be detected between the isolated patent ductus arteriosus and the patent ductus associated with other congenital heart malformations, the specimens were classified according to age (Table). On the basis of the findings in the reports concerning the time of anatomical closure of the ductus arteriosus, 4 age-groups were distinguished, as follows.

GROUP I

Three ducts of prematurely born infants, with a gestational period of 32, 35, and 36 weeks, who had lived for 2 days, 3 days, and 12 hours, respectively.

The first 2 cases (cases 1 and 2) showed histologically a stage of anatomical closing process normally begun, in accordance with their age (2 and 3 days after delivery). The ductus of the infant who lived for 12 hours (case 3) did not show the abovementioned characteristics of the normal closing process in that there were no intimal cushions or mucoid lakes, and the internal elastic lamina bordered the lumen (Fig. 5).

GROUP II

Fifteen ducts, ranging in age from immediately after full-term delivery to 1 week.

Except in cases 4 and 13, the structure of the ductus wall indicated a normal closing process. In one case (case 18) the ductus was almost closed. Case 13 showed the general characteristics of a normal closing ductus but also two large dissecting aneurysms in the wall. Case 4 showed a peculiar histological anomaly which is described in the next group.

GROUP III

Ten cases, ranging in age from 8 days to 2 months. Five of these ducts (cases 19, 20, 21, 23, 24) were patent, showing stages of an anatomical closing process normally begun. Two (cases 25 and 28) are almost closed, showing only a very small slit-like lumen, and 3 (cases 22, 26, and 27) were patent, showing an abnormality of the wall. One specimen in the last group (case 26) showed a wall structure resembling an elastic artery rather than a muscular artery (Fig. 6). In this case the elastic lamellae of the aorta and pulmonary artery continued into the ductus wall except in a small central part of the media, whereas normally about two-thirds of the elastic lamellae merge into the adventitia of the ductus and the remaining lamellae form the internal elastic lamina (Fig. 5). In the remaining 2 cases (cases 22 and 27) and in case 4 of group II, the histological structure of the wall did not differ greatly from the picture shown by a normally closing ductus at first sight, but on closer inspection there was a remarkable feature: a conspicuous wavy unfragmented subendothelial elastic lamina (Fig. 7 and 8) over most of the intimal cushions and merging into the normal internal elastic lamina of the duct where no intimal cushions were present.

GROUP IV

Fourteen cases, ranging in age from 4 months to 32 years. All these ducts had a histologically abnormal wall. Ten (see Table) showed, as the most striking feature, the unfragmented wavy subendothelial elastic lamina (Fig. 9 and 10). In general, the intimal cushions were not very pronounced and the internal elastic lamina underneath them was often not fragmented (Fig. 10). In 7 of these cases there was no increase in the amount of elastic material in the intima or media compared with the normally closing ductus, and 3 showed a media and intima with slightly more elastic material than normal. It is not possible, however, to count the elastic lamellae as in elastic arteries. In 3 other cases, the duct showed a pronounced increase in the amount of elastic tissue with countable elastic lamellae, only the central part of the media containing slightly less elastic material. In 2 (cases 30 and 36) a few not very prominent intimal cushions were also present, and these again showed the subendothelial elastic lamina. The third case (case 31) bore a strong resemblance to case 26 in group III, looking more like an elastic than a muscular artery. No intimal cushions or internal elastic lamina were present, but a subendothelial elastic lamina was discernible. The fourteenth case (case 39) was remarkable in that the pulmonary end of the ductus was almost closed, showing all of the features of a normal closing process, whereas the aortic end was widely patent and showed the subendothelial elastic lamina (Fig. 11).

Discussion

In all cases with a patent ductus at an age of 4 months or older (group IV) the wall showed a histological picture which differed from that seen during the normal closing process. In the age group from 1 week to 2 months (group III) the wall structure either reflected a normal closing process or showed an abnormality. The same holds for groups I and II.

On the basis of published data (Cassels, 1973), it seems justified from a clinical point of view to speak of persistent ductus arteriosus in all cases of patent ductus in infants older than 3 months. Since these cases always show an abnormal histo-

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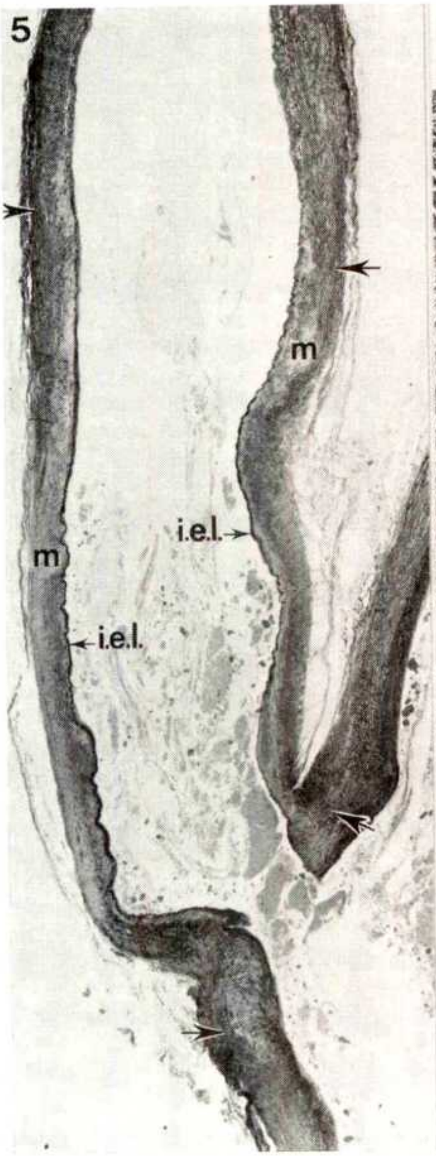

Fig. 5 *Section showing ductus arteriosus and adjacent great arteries. No characteristic features of the onset of the anatomical closing process are present. The merging of the greater part of the elastic lamellae of the adjacent elastic arteries into the adventitia of the ductus arteriosus (→) is clearly visible, the remainder forming the internal elastic lamina. Case 3, prem. 36 weeks, lived 12 hours. (Weigert elastic stain. ×13·5.)*

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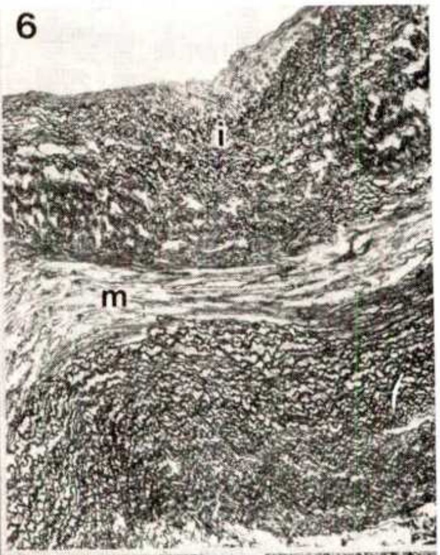

Fig. 6 *Detail of a transverse section of a ductus arteriosus showing aortification. In the intima and the outer part of the media many countable elastic lamellae are present. No subendothelial elastic lamina is seen. Case 26, 2 months. (Weigert elastic stain. ×32.)*

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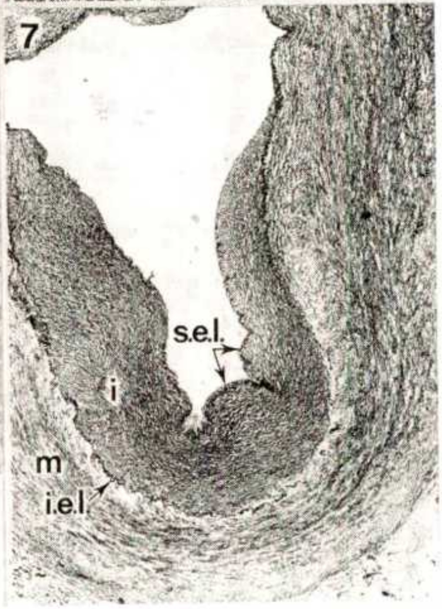

Fig. 7 *Transverse section of a ductus arteriosus, showing a subendothelial elastic lamina on top of the intimal cushions. Intima and media contain slightly more than the normal amount of elastic material. Case 22, aged 17 days. (Weigert elastic stain. ×28.)*

logy, the histologist (e.g. the present author) will be inclined to define persistent ductus arteriosus on the basis of this abnormality. The clinician, however, will encounter difficulties if he does this, because the abnormal histology is not restricted to patients older than 3 months. This raises the problem of how to differentiate clinically between persistent ductus and 'simple' prolonged patency in infants younger than 3 months. The pharmacological treatment of prolonged patency might throw some light on this problem. It is conceivable that a persistent ductus arteriosus with an abnormal histology of the wall, would not react to certain drugs, e.g. indomethacin, which induce closure in cases of 'simple' prolonged patency. If this working hypothesis should prove to be correct, the term persistent ductus arteriosus could be used for all cases of patent ductus in patients over 3 months of age and younger infants who do not react to, for example, indomethacin. Heymann *et al.* (1976) mentioned that one of 15 cases of prolonged patency in premature infants did not react to indomethacin. Histological investigation of such ducts might reveal an abnormality. Further investigations are required to elucidate this problem.

The 3 premature ducts studied did not provide

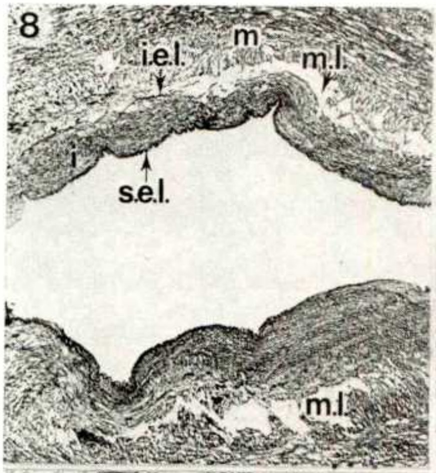

Fig. 8 *Transverse section of a ductus arteriosus. The lumen is bordered by a subendothelial elastic lamina. Case 4, 0 hours. (van Gieson elastic stain ×28.)*

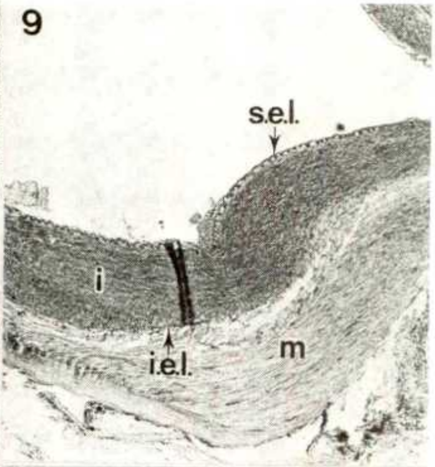

Fig. 9 *Detail of a transverse section of a ductus arteriosus, showing the wavy unfragmented subendothelial elastic lamina on top of an intimal cushion. Case 34, aged 8 months. (Weigert elastic stain. ×28.)*

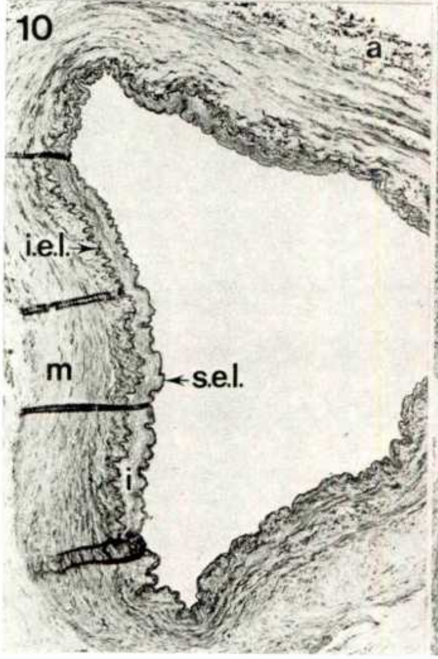

Fig. 10 *Transverse section of a ductus arteriosus. The intimal cushions are not very pronounced and the internal elastic lamina is not fragmented. Bordering the lumen, there is a subendothelial elastic lamina. Case 40, aged 5 years. (Weigert elastic stain. ×28.)*

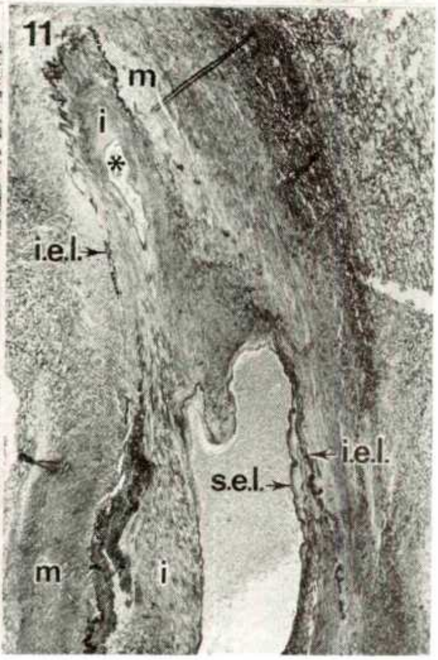

Fig. 11. *Section of a ductus arteriosus. The pulmonary end (*) is almost closed, whereas the aortic end is patent, showing the subendothelial elastic lamina. Case 39, aged 4 years. (Weigert elastic stain. ×14.)*

enough information to draw conclusions on the often prolonged patency of the ductus of prematurely born infants. As already mentioned, two of the specimens show that the closing process had begun normally. In the third no features of anatomical closure are present, but the wall does not show any other abnormalities. Though the problem of prolonged patency of the ductus in premature infants has been discussed in many publications (Rudolph *et al.*, 1961; Danilowicz *et al.*, 1966; Girling and Hallidie-Smith, 1971; Benjamin and Wiegenstein, 1972; Kitterman *et al.*, 1972; Friedman *et al.*, 1976; Heymann *et al.*, 1976; Nadas, 1976), I have undertaken a more detailed study with emphasis on the morphological aspects, which is now in progress.

The majority of the cases with an abnormal histology of the ductus wall show a pronounced wavy unfragmented subendothelial elastic lamina. Mucoid lakes may occur, but cytolytic necrosis is rarely encountered. There is usually no obvious increase in the amount of elastic material, so that superficially the wall does not differ greatly from that of a normally closing duct. This may account for the fact that some of the authors who studied cases with persistent ductus arteriosus state that the wall structure does not differ distinctly from that of a normally closing ductus (Wielinga, 1959; Bakker, 1962).

To the best of our knowledge, Jager and Wollenman (1942) are the only authors to mention the subendothelial elastic lamina, but they did not pay any further attention to this phenomenon. The fact that the subendothelial elastic lamina has not been described more often is in all probability explained by the lack, in the past, of histological studies in large series of persistent ductus arteriosus.

Mucoid lakes and cytolytic necrosis are also encountered during the normal closing process of the ductus arteriosus, but their significance is not known. Cytolytic necrosis is characterised by loss of nuclei (Fig. 3b); the accompanying increase of collagen fibres found by Schlatmann (1973) in aortic walls, was not seen in the present material.

Desligneres and Larroche (1970), who investigated 9 cases of patent ductus arteriosus in infancy as well as a large series of normal ducts, encountered 'more and thicker elastic fibres than usual' in the media for two cases of 'pathologic' ductus arteriosus and of one normal duct. Bakker (1962) also mentions an increase in the amount of elastic material in the wall of some specimens of patent ductus; he uses the term aortification to indicate this increase. A similar term, aorticisation, is used by Hutchins and Bannayan (1971) to indicate the development of endocardial fibroelastosis after myocardial infarction. This process, in which the endocardium is thickened and elastic lamellae appear, takes one to two years.

In our material we encountered in some ducts slightly more very fine elastic fibres than are found in normal closure (Table, Fig. 7). However, on a few occasions we saw a ductus wall with true elastic lamellae (Table; Fig. 6). For these cases, which constitute a very small minority, the term aortification can be used, indicating that the ductus wall resembles an elastic rather than a muscular artery. However, it should be stressed that we prefer to use the term only descriptively and regardless of the cause and time of development of the anomaly,

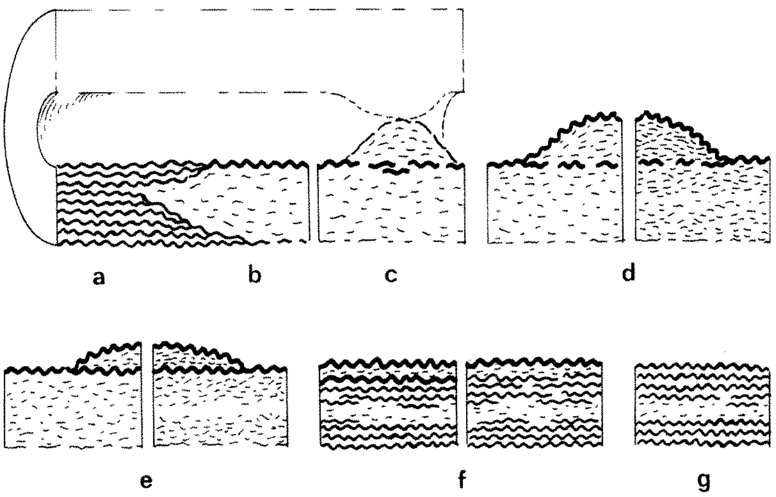

Fig. 12 *Distribution of elastic material in an elastic artery and in various types of patent ductus arteriosus: (a) elastic artery; (b) ductus arteriosus without intimal cushions; (c) ductus showing characteristics of normally begun closing process; (d) persistent ductus arteriosus with subendothelial elastic lamina and obvious intimal cushions, in some places showing a slight increase in the amount of elastic material in the intima and media; (e) persistent ductus arteriosus as in (d), but intimal cushions not very distinct and internal elastic lamina not fragmented; (f, g) persistent ductus arteriosus with aortification of the wall.*

because no relation between the duration of the patency and the amount of elastic material has been established. Fig. 12 gives a schematic representation of the distribution of elastic material in the various types of ductus wall structure.

A remarkable case is the one in which the pulmonary end of the ductus is almost closed, whereas the aortic end is patent and shows the subendothelial elastic lamina. The phenomenon of divergent behaviour of the aortic and the pulmonary ends of the ductus has been described (e.g. Bakker, 1962; Cassels, 1973). Cassels (1973: p. 311) states on the basis of his interpretation of studies done by Congdon (1922) and Keibel and Mall (1912), that this may have a developmental cause, since the ductus (6th branchial artery) originates from a ventral and a dorsal sprout; Cassels was of the opinion that 'the factors related to closure may affect the dorsal and the ventral sprout differently, allowing one or the other to remain open, the opposite segment closing normally'.

As to the question of whether the histological abnormality of the wall in persistent ductus arteriosus is secondary to the prolonged patency or part of a primary anomaly, a few points should be taken into consideration.

As indicated by the material studied (Table), there is no direct relation between age (i.e. the duration of the patency) on the one hand and the occurrence of the subendothelial elastic lamina as well as the amount of elastic material in the ductus wall, on the other hand. (The fact that we did not find many cases with an abnormal histology at a very early age will be dealt with later.) Furthermore, no relation was found between the presence of a subendothelial elastic lamina and the amount of elastic material in the intima and media. Therefore, the occurrence of a postnatal reaction of the ductus wall resembling the process described by Hutchins and Bannayan (1971), in which elastic lamellae are deposited in the endocardium over a period of one or two years after a myocardial infarction, seems improbable when cases with persistent ductus arteriosus of different ages are compared.

The altered haemodynamic situation in serious congenital heart malformations is apparently not adequate to maintain the patency of the duct. The cases with a patent ductus arteriosus associated with other congenital heart malformations are evenly distributed over the material. All too often, the ductus closes even in cases where patency would have meant survival. Another factor, e.g. a primary anomaly, must play a role. The fact that in isolated persistent ductus arteriosus, which is necessarily a primary defect, the same histological picture is found as in persistent ductus arteriosus in combination with other heart malformations, also suggests the existence of a primary abnormality.

The phenomenon that the anomaly can be restricted to one of the two sprouts from which the ductus originates (Cassels, 1973: p. 311) can be interpreted as support for the hypothesis of a primary defect of the ductus wall. Otherwise, we would have to accept that the two original components of the ductus are still differentiated, showing different reactions, a long time after the development of the ductus as a homogeneous structure.

In the present material only two young cases show the abnormal histology. One (case 4) is a neonate who died during delivery, and the other (case 22) lived 17 days. If a primary defect were involved, one would expect to find the abnormality evenly distributed over the different age-groups. However, this study was done on necropsy material, and probably there are very young infants with the anomaly who are still alive. Patients with solitary persistent ductus arteriosus do not as a rule die immediately after birth, and when it occurs in association with other congenital heart malformations it may prolong survival. Therefore, the fact that we did not find more cases showing a histologically abnormal ductus at a very early age does not necessarily mean that the difference in wall structure is a consequence of the prolonged patency.

From the above points, we can summarise as follows: (a) no relation between the duration of the patency and the amount or distribution of the elastic material, (b) altered haemodynamic situation inadequate to maintain patency, (c) the same histology in isolated persistent ductus arteriosus as when associated with other heart malformations, (d) one end of the ductus closing normally, the other end remaining patent, showing an abnormality, and (e) an abnormal histology in a neonate dying during delivery. From this we conclude that in all probability the aberrant distribution of elastic material, with the presence of a subendothelial elastic lamina as its most striking aspect, forms part of a primary anatomical defect of the ductus wall resulting in a persistent ductus arteriosus.

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Infradiaphragmatic total anomalous pulmonary venous return

Review of clinical and pathological findings and results of operation in 28 cases[1]

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Twenty-eight cases of infradiaphragmatic total anomalous pulmonary venous return are presented, 17 without associated complex intracardiac anomalies (group A), and 11 with additional complex lesions (group B). The anomalous site of connection was to the portal vein in 19 cases (68%), to the inferior vena cava in 4 (14%), the ductus venosus in 2 (7%), to the left hepatic vein in 2 (7%), and unknown in one. A patent foramen ovale was present in 82 per cent of cases in group A and 40 per cent in group B and was frequently associated with a small left atrium and left ventricle. Nine cases (8 in group A; 1 in group B) had surgical correction, with 3 long-term survivors. The surgical mortality was 66 per cent. The postoperative haemodynamic status of the 3 surving patients is very satisfactory, though 1 has a residual atrial septal defect. Factors which adversely affected the surgical outcome were: (1) a critically ill infant, (2) small left atrium and left ventricle, (3) a patent foramen ovale rather than atrial septal defect, (4) systemic arterial oxygen saturation less than 70 per cent, and (5) pulmonary arterial pressure in excess of systemic arterial pressure. The mortality for the entire series was 93 per cent.

Infradiaphragmatic total anomalous pulmonary venous return is a rare form of congenital heart disease. Because of obstruction to pulmonary venous return these children present in the first few weeks of life with cyanosis, pulmonary oedema, and right heart failure. Medical management is unsuccessful; surgical treatment is difficult and there have been only sporadic successes.

It is the purpose of this review to present our experience with this malformation discussing the clinical, pathological, and surgical aspects, in the hope of defining guidelines for diagnosis and successful surgical management.

Subjects and methods

We have reviewed the clinical records, including data from cardiac catheterisation studies and, where indicated, the necropsy records of 28 patients with infradiaphragmatic total anomalous pulmonary venous return seen at Texas Children's Hospital between 1957 and August 1975.

Cases of the mixed type of total anomalous pulmonary venous return were excluded from this review, as well as those with only partial anomalous venous return.

Cases were classified into two groups on the basis of associated intracardiac malformations. *Group A* (isolated infradiaphragmatic total anomalous pulmonary venous return) consisted of 17 patients with only a patent foramen ovale or atrial septal defect, and frequently a persistent ductus arteriosus. *Group B* (complex) consisted of 11 patients with infradiaphragmatic total anomalous pulmonary venous return who had other major intracardiac anomalies.

Ten cases in group B are discussed only from the viewpoint of the pathological anatomy and the association of splenic anomalies. The remaining case in this group is included in the review of cardiac catheterisation findings and surgical results. The clinical presentation, electrocardiograms, chest *x*-ray films, echocardiograms, cardiac catheterisation data, and surgical outcome of cases in group A

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Table 1 *Infradiaphragmatic total anomalous pulmonary venous return: anatomical findings*

	Group A Isolated	*Group B Complex*	*Per cent of total*
Site of anomalous venous connection			
Portal vein	11	8	68
Ductus venosus	2	0	7
Inferior vena cava	2	2	14
Left hepatic vein	1	1	7
Unknown	1	0	4
Type of interatrial communication			
Patent foramen ovale	14	5	68
Atrial septal defect	3	5	28
Common atrium	0	1	4
Ductus arteriosus			
Widely patent	9	1	36
Probe patent	2	1	11
Patent (unspecified size)	4	3	25
Closed	2	4	21
Unknown	0	2	7
Total	17	11	100

are presented in some detail.

Fourteen patients in group A had a cardiac catheterisation performed. Eleven of these and the case from group B had adequate haemodynamic records. The systemic arterial systolic pressure and oxygen saturation were compared with the pulmonary arterial systolic pressure and oxygen saturation in each case. Pulmonary hypertension was defined as a pulmonary arterial systolic pressure which was more than 50 per cent of systemic arterial systolic pressure. The pulmonary arterial oxygen saturation was considered equal to the systemic arterial oxygen saturation if there was no greater than two percentage points difference in oxygen saturation.

Eight patients in group A and 1 patient in group B had a surgical operation. Two patients from group A and the 1 from group B have had a postoperative cardiac catheterisation.

A necropsy was performed on 22 of the 25 patients who died. The development of left heart structures in patients from group A is further discussed in relation to the size of the interatrial communication and the ultimate surgical outcome. When describing the interatrial communication, use of the term atrial septal defect implies a larger opening than patent foramen ovale as evaluated at cardiac catheterisation, operation, or necropsy.

Results

SITES OF CONNECTION (Table 1)

In 19 cases (68%) the anomalous pulmonary venous connection was to the portal vein: this high frequency was similar in both groups A and B. Four patients had connection to the inferior vena cava, 2 to the ductus venosus, and 2 to the left hepatic vein. In 1 case from group A, infradiaphragmatic total anomalous pulmonary venous return was seen angiographically but the exact site of connection was not defined; a necropsy was not obtained in this case.

INTERATRIAL COMMUNICATION (Table 1)

Fourteen cases from group A had a patent foramen ovale rather than an atrial septal defect. On the other hand, out of a total of 8 cases with an atrial septal defect 5 were from group B. One case in group B had a common atrium.

DUCTUS ARTERIOSUS (Table 1)

Twenty cases (72%) out of the total group had a persistent ductus arteriosus. In 10 of these the ductus was widely patent and in 3 probe patent. A further 7 cases had a persistent ductus arteriosus but its size was not described.

LEFT ATRIUM AND LEFT VENTRICLE (Table 2)

Eleven cases in group A with a patent foramen ovale had small left heart chambers; the left atrium especially was underdeveloped. Of 3 cases in group A with an atrial septal defect, 2 had a left atrium and left ventricle of normal size.

Table 2 *Size of the left heart chambers related to type of interatrial communication (Group A patients)*

	Reduced	*Slightly reduced*	*Normal*	*Unknown*
Patent foramen ovale	8	3	1	2
Atrial septal defect	0	1	2	0
Total	8	4	3	2

ASSOCIATION OF SPLENIC ANOMALIES (Table 3)

Six cases in group B had asplenia, 3 a normal spleen, and in 2 cases the splenic status was unknown. The associated cardiac malformations are listed in Table 3. In group A, comment was made on the spleen at necropsy in 8 cases; a bilobed spleen in one case was the only abnormality noted.

CLINICAL FINDINGS (Group A)

The male to female sex ratio was 3:1. The birthweights ranged from 2·0 kg to 3·9 kg with a mean of 3·1 kg. Only 1 infant was born prematurely at 35 weeks of gestation. The infants developed symptoms between the first and eighth day of life, with an average age at the time of onset of symptoms of 3 days. There was a mean delay from the time of

Table 3 *Infradiaphragmatic total anomalous pulmonary venous return and complex congenital heart disease (Group B patients)*

Interatrial communication		11
Persistent ductus arteriosus		5
Splenic status		
Asplenia		6
Endocardial cushion defect	2	
Transposition of great arteries	2	
Pulmonary atresia	2	
Mitral atresia	3	
Ventricular septal defect	3	
Truncus arteriosus	1	
Inferior vena cava drainage to left atrium	1	
Persistent left superior vena cava	3	
Dextrocardia	2	
Normal spleen		3
Endocardial cushion defect	1	
Double outlet right ventricle	1	
Mitral atresia	1	
Infundibular pulmonary stenosis	1	
Single A-V valve	1	
Transposition of great arteries	1	
Unknown		2
Single ventricle, dextrocardia	1	
Ventricular septal defect, persistent ductus arteriosus	1	
Total number of patients		11

onset of symptoms until admission to Texas Children's Hospital of 11 days with a range of 1 day to 7 weeks. A further mean delay of 6 days occurred between the time of admission and operation or death.

Feeding difficulty and slow weight gain were the most common presenting symptoms. Tachypnoea was the most constant sign. Mild to moderate cyanosis was present in all, but in 2 patients it was an inconstant feature and in only 1 was it described as being severe. Half of the patients had a grade 1-2/6 ejection systolic murmur best heard along the left sternal border. In 2 patients, a soft systolic murmur was heard only over the liver. The liver was enlarged 3·0 cm or more below the right costal margin in 13 patients, while in 4 the size of the liver was normal at the initial examination.

RADIOGRAPHS (Group A)
The cardiothoracic ratio was normal in 15 patients and increased in 2 patients. Thirteen patients had radiographic evidence of pulmonary oedema, 3 had normal lung fields, and in 1 case the pulmonary vascular markings were reduced.

ELECTROCARDIOGRAMS (Group A)
Sinus rhythm was present in all but 1 patient who had a wandering atrial pacemaker. Only 1 patient had right atrial enlargement. Right axis deviation of the QRS complex in the frontal plane was present in each case, ranging from +120° to +160°. Definite right ventricular hypertrophy was present in 12 of 14 available tracings with a qR pattern in the right chest leads in 6 of these. One tracing showed probable right ventricular hypertrophy. In 1 patient the electrocardiogram was interpreted as normal on the first day of life. A paucity of left ventricular forces was a striking abnormality in half of the patients.

ECHOCARDIOGRAMS (2 patients from group A and 1 patient from group B)
The left atrial and left ventricular dimensions were slightly reduced in two infants in the newborn period. The common pulmonary venous chamber was not identified and the right ventricular dimension was normal. A large right ventricle, paradoxical septal motion, and the common pulmonary venous trunk were noted in case B1 (Table 4).

CARDIAC CATHETERISATION (11 patients from group A and 1 patient from group B)
Systemic arterial oxygen desaturation was present in every case, the range of systemic arterial oxygen saturation for the group being 40 to 93 per cent. The mean systemic arterial oxygen saturation was 65 per cent in the group of 8 patients with only a patent foramen ovale and 80 per cent in those with an atrial septal defect. In 6 patients, 5 from group A

Table 4 *Clinical, haemodynamic, and necropsy data: correlation with surgical outcome*

•	*Age* *Days*	*Weeks*	*Weight (kg)*	*PAP/SAP × 100%*	*Systemic arterial oxygen saturation (%)*	*ASD or PFO*	*LA*	*LV*	*Anastomosis*	*Outcome*
Group A										
1	—	1	2·66	> 100	54	PFO	VS	VS	Widely patent	D 1 day
2	6	—	3·5	—	—	PFO	S	S	Widely patent	D 1 day
3	12	—	2·75	> 100	63	PFO	VS		Widely patent	D 1 day
4	9	—	3·0	100	70	PFO	S	S	Widely patent	D 1 day
5	—	6	2·9	> 100	77	PFO	S	S	Stenotic	D 1 day
6	—	4	3·0	90	62	PFO	S	S	Stenotic	D 3 months
7	—	8	3·2	60	93	PFO	—	—	Widely patent	A 13½ years
8	—	4	4·3	> 100	70	ASD	N	N	Widely patent	A 3½ years
Group B										
1	10 yrs		20·0	100	85	ASD	N	N	Widely patent	A 2 years

PAP = pulmonary arterial pressure; SAP = systemic arterial pressure; ASD = atrial septal defect; PFO = patent foramen ovale; LA = left atrium; LV = left ventricle; VS = very small; S = small; N = normal size; D = died; A = alive.

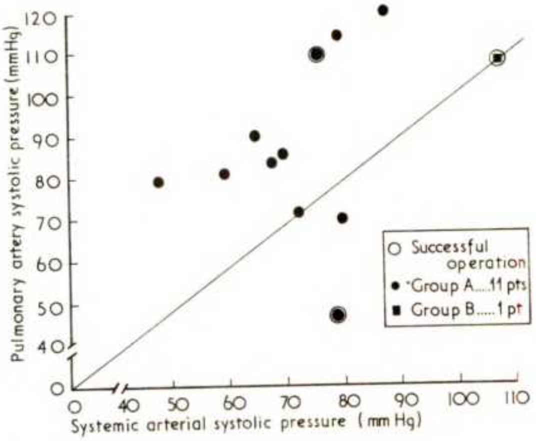

Fig. 1 *Comparison of pulmonary arterial systolic pressure with systemic arterial systolic pressure.*

and the 1 patient from group B, the saturations were similar in all cardiac chambers and in both great arteries. The oxygen saturation in the pulmonary artery was lower than aortic saturation in 4 patients and higher in 1.

All patients had raised pulmonary arterial pressure (Fig. 1). In 7 patients the pulmonary arterial pressure was higher than the systemic arterial pressure, in 2 patients the pressures were equal, and in the remaining 2 patients the pulmonary arterial pressure was lower than the systemic arterial pressure.

Two patients, cases B1 and A7, had at least intermittently nonobstructive anomalous pulmonary venous drainage to the inferior vena cava and had pulmonary arterial pressures which were 100 per cent and 60 per cent of systemic, respectively. The systemic arterial oxygen saturation in these 2 cases was 85 per cent and 93 per cent, respectively. Both had successful operations.

SURGICAL CORRECTION (Table 4)

Eight patients in group A and 1 patient in group B had operations for correction of infradiaphragmatic total anomalous pulmonary venous return. Table 4 relates surgical outcome to the relevant clinical, haemodynamic, and anatomical features in these cases.

The average age of the patients in group A at the time of operation was 20 days, with a range of 6 days to 8 weeks. The patient in group B (B1), who survived operation, was 10 years of age at the time of diagnosis and surgical correction (Duff *et al.*, 1975). The average weight of the patients in group A was 3·2 kg (2·66 to 4·3 kg). Those who survived operation in this group had an average weight of 3·5 kg.

Five patients died in the immediate postoperative period from low output failure. In 2 patients the patent foramen ovale was closed surgically and in 3 it was left open. At necropsy, the left atrium was small in each of these patients and very small in 2 patients. The left ventricle was also small in 3 patients, being hypoplastic in 1 patient.

Two patients died as a result of stenosis at the site of surgical anastomosis, one (A5) in the immediate postoperative period and the other (A6) 3 months after operation.

Three patients, 2 from group A and 1 from group B are alive and well, 13½ years (A7), 3½ years (A8), and 2 years (B1) from the time of surgical correction.

POSTOPERATIVE CARDIAC CATHETERISATION

The postoperative haemodynamic data in the 3 long-term survivors are shown in Table 5. All 3 are asymptomatic. Almost complete resolution of pulmonary hypertension has taken place and each has normal systemic arterial oxygen saturation.

The interatrial communication was closed at operation in 2 of the long-term survivors. In patient A8, the atrial septal defect was not closed and now

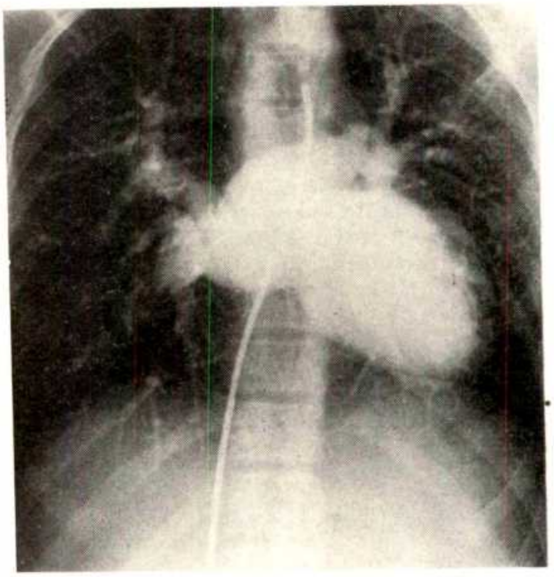

Fig. 2 *Case A7. Angiogram shows a normal left atrium and left ventricle after injection of contrast medium into the main pulmonary artery. All pulmonary venous return is to the left atrium, with no residual infradiaphragmatic drainage. The pulmonary veins are mildly dilated.*

at 3½ years of age he has a left-to-right shunt with a pulmonary to systemic flow ratio of 2·5:1. An angiogram (Fig. 2) on patient A7 13½ years after corrective operation showed a left atrium and left ventricle of normal size; the pulmonary veins, which are slightly distended, all drain to the left atrium.

Discussion

Total anomalous pulmonary venous return comprises 1 to 3 per cent of all congenital heart lesions (Keith *et al.*, 1967; Bharati and Lev, 1973). The anomalous connection and drainage is below the diaphragm in 10 to 20 per cent of these cases (Burroughs and Edwards, 1960). The frequency of drainage to different anatomical infradiaphragmatic sites in our series is similar to that reported by others, with 68 per cent connecting to the portal vein (Burroughs and Edwards, 1960; Bonham Carter *et al.*, 1969). Associated complex cardiac lesions have been noted in 20 to 30 per cent of patients with total anomalous pulmonary venous return (Burroughs and Edwards, 1960). When the connection is below the diaphragm the incidence of these anomalies is increased to approximately 50 per cent (Lucas and Schmidt, 1968). In the present series, 40 per cent of the cases had associated complex intracardiac anomalies.

Splenic anomalies, especially asplenia, are common in total anomalous pulmonary venous return when this is associated with complex cardiac lesions (Bharati and Lev, 1973; Delisle *et al.*, 1976). In the present series, two-thirds of the cases in group B had asplenia and one-third had a normal spleen. Anomalies of the spleen are rare in the absence of complex cardiac defects; a bilobed spleen in 1 case was the only anomaly noted in 8 group A patients.

Cardiac output and the development of the left atrium and left ventricle in isolated infradiaphragmatic total anomalous pulmonary venous return depend on the size of the interatrial communication (Burroughs and Edwards, 1960). Graham *et al.* (1972), using biplane cineangiography, showed that the volume of the left atrium was reduced in all patients with all types of total anomalous pulmonary venous return, but left ventricular volume was reduced in only one-third of their cases. Only 3 of their patients, however, were less than 2 months of age and the majority had nonobstructive total anomalous pulmonary venous return. With obstruction to pulmonary venous return and a patent foramen ovale one would expect the hypoplasia of the left atrium and the left ventricle to be exaggerated. The pathological observations in the present series and in that of Bharati and Lev support this contention (Bharati and Lev, 1973).

The clinical presentation of total anomalous pulmonary venous return, irrespective of the site of connection, is determined chiefly by the presence or absence of obstruction to pulmonary venous drainage. When the connection is infradiaphragmatic some degree of obstruction to blood flow is almost always present. The causes of obstruction in this situation have been reviewed elsewhere (Burroughs and Edwards, 1960; Hastreiter *et al.*, 1962; Tynan *et al.*, 1974; Delisle *et al.*, 1976). Three of the patients in this series with isolated infradiaphragmatic total anomalous pulmonary venous return had at least intermittently nonobstructive drainage: 2 of these had connection to the inferior vena cava, and 1 to the portal vein with a large persistent ductus venosus. The clinical picture in the presence of obstruction is characteristic (Lucas and Schmidt, 1968). However, it is important to emphasise that cyanosis may not be prominent and may be intermittent. In addition, the liver may be of normal size and occasionally a murmur may be audible over it.

The chest *x*-ray usually supports or even suggests the diagnosis of obstructed pulmonary venous return with a diffuse hazy granular pattern of pulmonary oedema and normal heart size; however, the lung vascularity may occasionally appear normal or even reduced. This latter finding was noted in 1 of our patients and has also been described by Friedli *et al.* (1971). When pulmonary venous obstruction is severe, leading to pulmonary hypertension, the presence of a persistent ductus arteriosus allows right-to-left shunting which further reduces pulmonary blood flow producing normal or oligaemic lung fields on *x*-ray. These infants are very cyanotic; the systemic arterial oxygen saturation in our patient was 40 per cent and in the reported patient of Friedli *et al.* 32 per cent. When obstruction is intermittent, there may be considerable variation in the lung vascular markings over a period of a few hours. Therefore, repeated observations are of considerable importance in evaluating these patients. Radiographic differentiation from neonatal pneumonia, hyaline membrane disease, aspiration syndrome, and pulmonary haemorrhage may be difficult at times (Johnson *et al.*, 1958). However, from a clinical standpoint, infants with these conditions usually show signs of improvement with increasing age, while those with obstructed total anomalous pulmonary venous return deteriorate.

The electrocardiogram was helpful in supporting the diagnosis and almost invariably showed right ventricular hypertrophy (Gathman and Nadas, 1970; Rudolph, 1974). A qR pattern in the right praecordial leads and reduced positive electrical forces in the left praecordial leads were noted in half of our cases. Both these features were present in patients with pulmonary hypertension, but did not distinguish those with moderate from those with severe pulmonary hypertension.

Echocardiographic criteria for the diagnosis of total anomalous pulmonary venous return, especially the cardiac and supracardiac varieties, have been outlined by Paquet and Gutgesell (1975) from this institution. We did not find the echocardiogram to be diagnostic, however, in 2 infants with infradiaphragmatic total anomalous pulmonary venous return. In patient 1 from group B, who was 10 years of age, the common pulmonary venous chamber was clearly seen dorsal to the left atrium as described by Paquet and Gutgesell. Its value in the infant with infradiaphragmatic total anomalous pulmonary venous return is primarily to exclude other causes of cyanotic congenital heart disease, such as transposition of the great arteries and tetralogy complexes. However, the demonstration of a small left atrium and perhaps also small left ventricle lends support to the diagnosis of anomalous pulmonary venous return.

Those patients with lower systemic arterial saturation at cardiac catheterisation, especially when this is below 70 per cent, and with pressure at systemic level or above in the pulmonary artery are likely to be obstructive in type. This has also been noted by others (Gathman and Nadas, 1970; Delisle *et al.*, 1976). In determining the site of connection of the anomalous trunk, variation in oxygen saturation between the inferior vena cava and the rest of the heart was inaccurate and unreliable. In general, however, the infants were not catheterised through the umbilical vein which would have facilitated more direct sampling of pulmonary venous blood from the portal vein (Sneed, 1972). Alternatively, manipulation of the catheter into the hepatic vein should be attempted in all instances when the catheterisation is from the femoral vein as a high oxygen saturation at that site would be diagnostic of anomalous return either to the hepatic or to the portal vein.

For precise diagnosis, angiography is essential. As suggested by Tynan *et al.* (1974), if the anomalous trunk can be entered directly through its site of connection, e.g. to the portal vein, then injection of contrast medium into the common channel gives excellent anatomical definition of the whole pulmonary venous tree. Failing this ideal, selective branch pulmonary artery injections are much more useful than a main pulmonary artery injection. From the latter site, in the presence of severe pulmonary hypertension, most of the contrast medium is lost through the persistent ductus arteriosus, which was patent in 82 per cent of isolated cases in our series. It is also important to continue the cineangiogram for 10 seconds or more to allow the contrast medium to circulate through the pulmonary vascular bed. An effort should be made to visualise all pulmonary veins, as there is often considerable variation in the site of attachment of individual veins to the common pulmonary venous channel. This has important surgical consequences as one or more pulmonary veins may be overlooked and continue to drain into the systemic venous circulation after distal ligation of the common channel (e.g. case B1, Table 5).

There is little argument that the proper management of isolated obstructed infradiaphragmatic total anomalous pulmonary venous return is surgical. The operation should be performed as an emergency as

Table 5 *Postoperative cardiac catheterisation data*

Patient	*Site of drainage*	*Age*		*Haemodynamic data*								*Comment*
				Preoperative				*Postoperative*				
		Operation	*Present*	*Oxygen saturation (%)*		*Pressure (mmHg)*		*Oxygen saturation (%)*		*Pressure (mmHg)*		
				PA	*Systemic A*	*PA*	*Systemic A*	*PA*	*Systemic A*	*PA*	*Systemic A*	
A7	IVC	8 wk	13½ yr	86	93	45/16	80/35	78	98	30/15	—	No residual defects
A8	Portal vein	4 wk	3½ yr	63	70	100/50	80/50	78	96	28/12	100/0 10 (LV)	Residual atrial septal defect with $\dot{Q}p/\dot{Q}s$ 2.5:1
B1	IVC	10 yr	12 yr	85	85	110/58	110/80	76	98	45/11	105/76	Residual drainage of inferior left pulmonary vein to inferior vena cava but no step-up in oxygen saturation; mild tricuspid regurgitation

$\dot{Q}p/\dot{Q}s$ = ratio of pulmonary to systemic blood flow.

soon as the diagnosis is made, since these infants may deteriorate rapidly. There is an almost 100 per cent mortality with medical management, the majority of infants dying before 6 months of age (Keith *et al.*, 1967). In the presence of obstruction which is not at atrial level, balloon septostomy is not recommended at the time of cardiac catheterisation (El-Said *et al.*, 1972). Though surgical mortality is high and successes still worth reporting, excellent results can be achieved as shown by the 3 long-term survivors in this series. Including the patients in this review, 21 patients have had successful corrective operations for infradiaphragmatic total anomalous pulmonary venous return (Cooley and Balas, 1962; Sloan *et al.*, 1962; Woodwark *et al.*, 1963; Cooley *et al.*, 1966; Jeiger *et al.*, 1967; Llewellyn *et al.*, 1968; Mody *et al.*, 1969; Barratt-Boyes *et al.*, 1971; Friedli *et al.*, 1971; Joffe *et al.*, 1971; Buckley *et al.*, 1972; Barratt-Boyes, 1973; Breckenridge *et al.*, 1973; Higashino *et al.*, 1974). During follow-up, which has varied from 2 weeks to 13 years, 2 of these patients have died. The others were stated to be well at last evaluation, though only 2 have had haemodynamic evaluation postoperatively (Jeiger *et al.*, 1967; Higashino *et al.*, 1974).

The factors which contributed to the high mortality and militated against successful surgical outcome in the present series were:

(1) Critically ill infants: this was often because of delay in clinical recognition of heart disease before hospital admission and delay in definitive diagnosis after admission.

(2) A patent foramen ovale rather than an atrial septal defect: this was frequently associated with a small left atrium and left ventricle, which we felt contributed significantly to low output failure and death in 5 patients in the immediate postoperative period.

(3) Systemic arterial oxygen saturation less than 70 per cent.

(4) A pulmonary arterial pressure greater than systemic arterial pressure.

It seems also, both from the volume studies of Graham *et al.* and our subjective impression, that further reduction in the size of the small left atrium by primary closure of the intra-atrial communication is contraindicated.

Conclusion

With careful attention to clinical detail, critical radiographic evaluation, especially analysis of *x*-ray films taken at intervals of a few hours coinciding with alteration in clinical signs, supportive electrocardiographic and echocardiographic findings, the diagnosis of total anomalous pulmonary venous return should at least be suspected. With this suspicion, cardiac catheterisation is performed to confirm the diagnosis and define the exact anatomical site or sites of connection and drainage. In this way, unnecessary delays can be avoided and operation performed when the infant is in the most stable cardiac and metabolic state.

Addendum

Since initially submitting this paper, we have had 3 additional newborn infants with isolated obstructive infradiaphragmatic total anomalous pulmonary return. One died while being prepared for operation and another died within 24 hours of surgical correction; the remaining patient had successful surgical correction at 5 days of age and is clinically well 2 months later.

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Ultrasound study of dynamic behaviour of left ventricle in genetic asymmetric septal hypertrophy

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Genetic asymmetric septal hypertrophy is a primary myocardial disease with characteristic echocardiographic features. Echocardiographic studies in patients have shown that the ventricular septum is a hypocontractile structure. Since overall cardiac systolic function in this disease is normal, the present study was undertaken to explain this phenomenon.

Nineteen patients with proven genetic asymmetric septal hypertrophy, and 15 patients with coronary artery disease and echocardiographic akinesis of the ventricular septum with an angiographically complete obstruction of the descending branch of the left coronary artery, were compared with 20 normal subjects.

Analysis includes calculation of systolic thickening of the septum and left ventricular posterior wall, calculation of systolic posterior wall velocity, and determination of left ventricular internal dimensions with ultrasound.

Results showed that the ventricular septum was a hypocontractile structure in asymmetric septal hypertrophy, whereas the left ventricular posterior wall seems to compensate for this as is seen by the augmented indices for systolic thickening and velocity of the posterior wall. Left ventricular size was small. This was in contrast to the findings in coronary artery disease with septal akinesia. Indices for thickening and velocity of the posterior wall were decreased, whereas left ventricular size was enlarged. We propose that systolic function of the left ventricle can be maintained by three different compensatory mechanisms; (1) increase of dimension (Starling mechanism); (2) increase in systolic thickening; and (3) increase in systolic velocity of contraction.

Genetic asymmetric hypertrophy of the interventricular septum is a primary myocardial disease with distinct morphological abnormalities (Henry *et al.*, 1973).

Several studies using electron microscopy have identified ultrastructural changes consisting of abnormal architecture of the interventricular septum with bizarrely shaped muscle cells (Ferrans *et al.*, 1972; Maron *et al.*, 1974).

Although one would expect these changes to result in an impaired overall cardiac function, this does not occur. Indeed, the systolic cardiac function in these patients is often normal (Goodwin and Oakley, 1972). In an attempt to clarify this enigma, an echocardiographic study was undertaken. In this study we paid special attention to the posterior wall of the left ventricle and analysed its contraction pattern in an effort to explain the existence of a normal overall cardiac systolic function in this disease.

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Patients and methods

Nineteen patients with genetic asymmetric septal hypertrophy, 11 women and 8 men, ages 14 to 53 years were studied.

The diagnosis was based on the echocardiogram (septal hypertrophy was defined as a thickness greater than 15 mm, and a ratio of septal to posterior wall thickness of greater than 2:1).

All patients underwent haemodynamic evaluation and left ventriculography. In 11 patients, a resting gradient across the left ventricular outflow tract was present and all patients had abnormalities consistent with asymmetric hypertrophy on their right anterior oblique left ventricular cine angiocardiogram. In addition, 15 patients with coronary artery disease, all having an angiographically complete obstruction of the descending branch of the left coronary artery and septal akinesia on their echocardiograms, were also studied.

As a control group 20 'normal' volunteers were

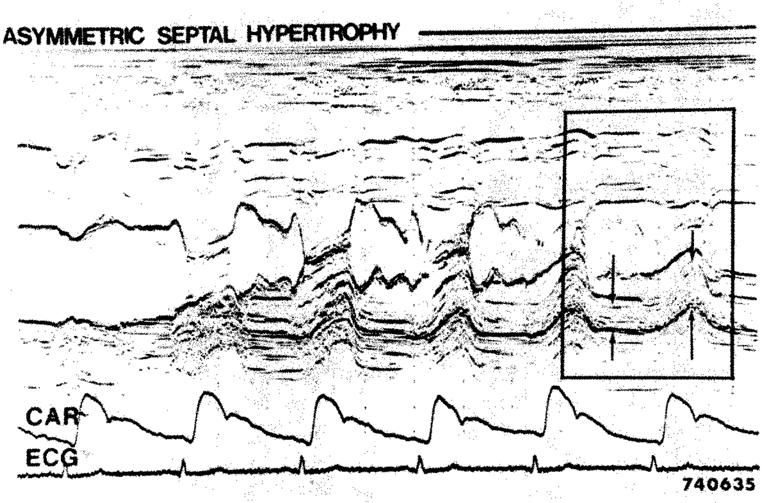

Fig. 1 *A standard M-mode sectorscan in a patient with haemodynamic proof of genetic asymmetric septal hypertrophy. The motion pattern of the anterior mitral leaflet is normal during systole, indicating no outflow obstruction. The area studied is that part of the left ventricle between the tips of the mitral valves and the papillary muscles. This is shown at the right of the picture. The two important features are that: (1) the motion of the interventricular septum is much reduced as is the systolic thickening and (2) the motion pattern of the left ventricular wall is increased and shows excessive thickening.*

used. ('Normal' was defined on the basis of the absence of complaints, clinical examination of the heart, electrocardiogram, and chest *x*-ray).

ECHOCARDIOGRAPHIC EXAMINATION

The ECHOcardioVISOR 01 (Organon Teknika, Oss, The Netherlands), which has both the conventional single and the recently developed two-dimensional imaging facilities was used (Kloster *et al.*, 1973; Roelandt *et al.*, 1974).

A 1·4 cm, 2·25 MHz transducer focused at 7·5 cm was employed and the M-mode echocardiograms recorded simultaneously with the electrocardiogram by a Honeywell Linescan-recorder (Visicorder 1856) on light-sensitive paper (Kodak Linagraph 1895). All patients were examined in the supine or slightly left lateral recumbent position, with the transducer placed as close as possible to the left side of the sternum and perpendicular on the chest wall until the characteristic pattern of motion of the anterior mitral valve leaflet was maximally recorded. The ultrasonic beam was then directed laterally and slightly inferiorly to define the 'standard area' of the left ventricle just distal to the tips of the mitral valve in which the motion of the interventricular septum and left ventricular posterior wall could be detected together. After the standard left ventricular echocardiograms, sector scans were made and recorded from the aortic root across the left ventricular cavity to the left ventricular apex. During the examination gain settings were continuously adjusted until the best available recordings could be made.

Fig. 1 shows a representative M-mode sector scan of a patient with genetic asymmetric septal hypertrophy without left ventricular outflow gradient under basal conditions during cardiac catheterisation. The disproportionate thickness of the interventricular septum compared with the left ventricular posterior wall thickness is striking. Furthermore, the motion of the interventricular septum is reduced compared with the increased motion of the left ventricular posterior wall.

In order to show the accuracy of the single element recordings another procedure was carried out. It is evident that a single beam recording does not show motion perpendicular to the sound beam axis

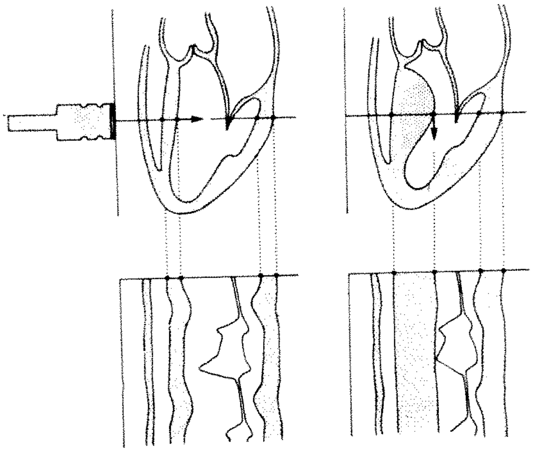

Fig. 2 *Motion of cardiac structures as recorded in M-mode (left side) is not seen when this motion is perpendicular to the sound beam (right side).*

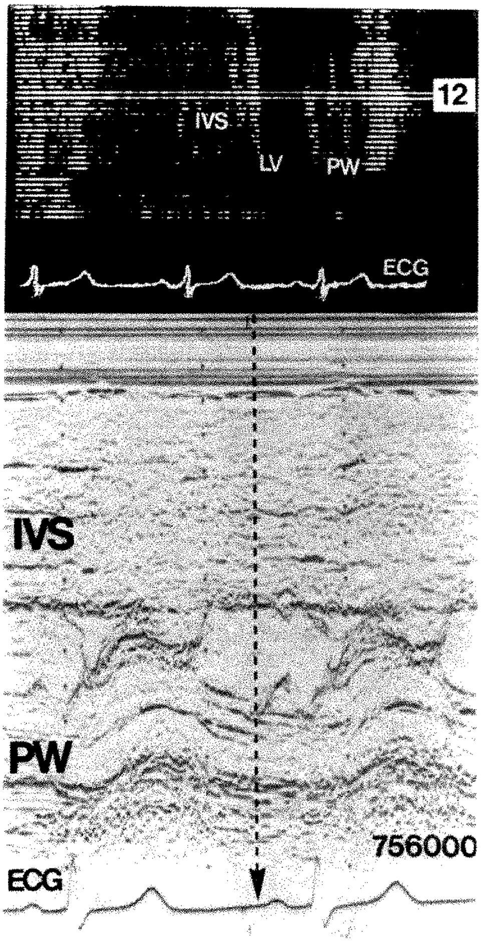

Fig. 3 *Stop-frame image in diastole obtained from a patient with outflow obstruction. A single crystal of the 20 crystal transducer at the level of the anterior mitral valve leaflet—labelled 12—is selected and its echo information is recorded in the M-mode and represented below. The dotted line shows the timing of the cross-sectional image within the cardiac cycle.*

(Fig. 2). Therefore, real time two-dimensional imaging was performed to observe this motion. This was done by selection of a single crystal out of the 20-crystal transducer at the level of the tip of the anterior mitral leaflet. A recording of this echo information in the M-mode is shown in Fig. 3.

This procedure was repeated using two elements —one above and one below the chosen one—in order to show that septal thickness is not changed by a vertical motion which could be seen from the two-dimensional real time images (Fig. 4). This procedure was included in the echocardiographic examination of all patients studied.

ANALYSIS OF ECHOCARDIOGRAPHIC DATA

The left ventricular internal diameter (D) was measured in mm from the left septal endocardium to the left ventricular posterior wall endocardium at end-diastole (Dd) and at end-systole (Ds) (end-diastole at the R-peak of the QRS complex and end-systole at the shortest dimension (ten Cate *et al.*, 1974)).

Septal and posterior wall thickness (T) was also measured at the same points of reference (Td = end-diastole and Ts = end-systole). Fractional or per cent systolic thickening of both interventricular septum and left ventricular posterior wall was determined as $\frac{\text{Ts}-\text{Td}}{\text{Td}} \times 100\%$ (in %) where Ts and Td are the systolic and diastolic thickness of either the interventricular septum or left ventricular posterior wall. Normalised posterior wall velocity was calculated as $\frac{\text{Ts}-\text{Td}}{\text{Td} \times \text{ET}}$, where ET is the ejection time measured from the onset to peak contraction (Cooper *et al.*, 1972) (see also Fig. 8).

Student's t test for independent observation was used to determine the statistical significance of these measurements (Fisher, 1970).

Results

The results of our measurements are summarised in the Table. Systolic thickening of the interventricular septum in the 3 groups of patients studied is shown in Fig. 5. Differences between the normal group and the patients with genetic asymmetric septal hypertrophy, as well as those with coronary artery disease, were statistically significant ($P < 0{\cdot}005$).

Table *Results of echocardiographic measurements (m ± SD)*

	Heart rate (beats/ min)	*IVS thickening (%)*	*LVPW thickening (%)*	*Normalised PW velocity*	*Dd (mm)*	*Ds (mm)*
N	72 ±6	42 ±8*	52 ±9*	1·2 ±0·2*	53 ±5*	38 ±4*
ASH	77 ±7	10 ±6*	70 ±30*	1·7 ±0·5*	41 ±10*	26 ±7*
CAD	70 ±8	15 ±12*	33 ±8*	1·3 ±0·4	63 ±11*	50 ±13

N, normal subjects; ASH, asymmetric septal hypertrophy; CAD, coronary artery disease; IVS interventricular septum; LVPW, left ventricular posterior wall; PW, posterior wall.
*P < 0·005.

Fig. 6 shows a typical example of a patient with asymmetric septal hypertrophy with a posterior wall systolic thickening of 100 per cent. In Fig. 7, the results of systolic thickening of the left ventri-

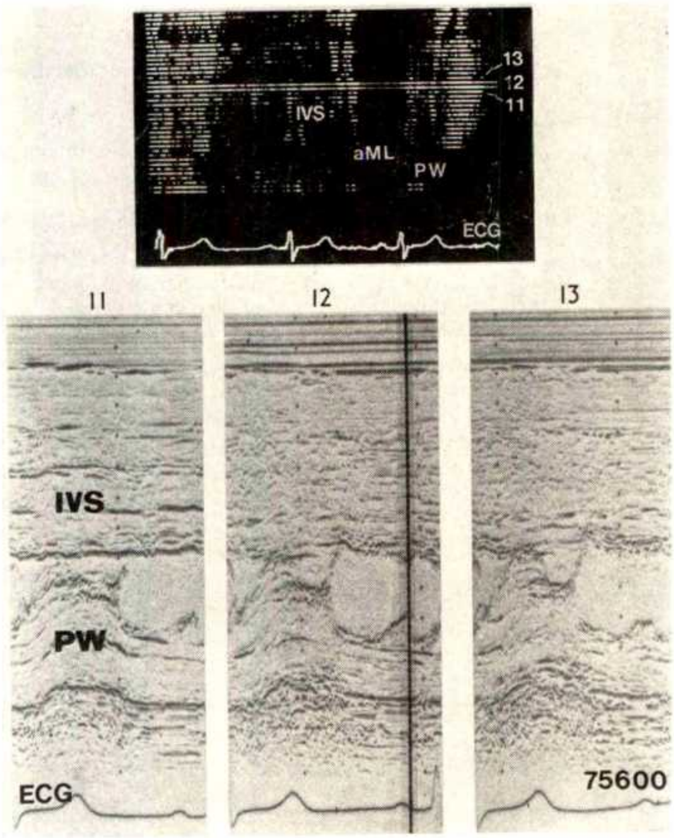

Fig. 4 *The procedure described for crystal 12 in Fig. 3 is repeated for crystal 11 and crystal 13. M-mode recording of these 3 consecutive elements shows no large difference in systolic thickening of the septum or the posterior ventricular wall, indicating that vertical motion seen on the real-time two-dimensional images does not influence quantitative measurements by single element echocardiography.*

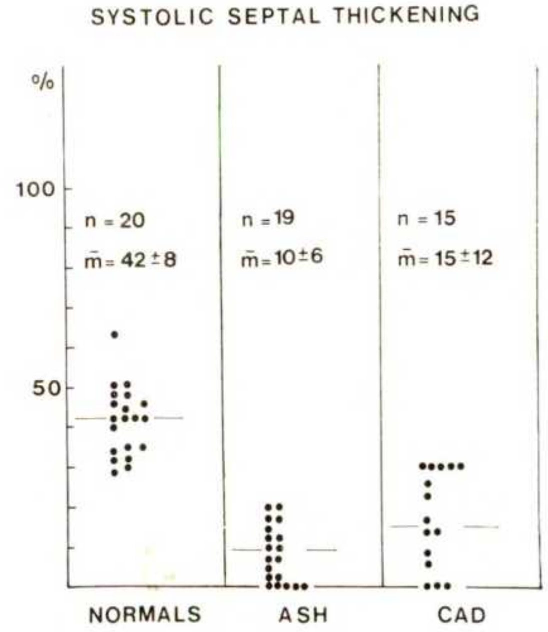

Fig. 5 *Systolic septal thickening in 20 normal subjects is 42 ± 8 per cent, 10 ± 6 per cent in 19 patients with genetic asymmetric septal hypertrophy, and 15 ± 12 per cent in 15 patients with coronary artery disease and septal akinesia. The difference between systolic septal thickening in normals and in patients with asymmetric septal hypertrophy or coronary artery disease is statistically significant ($P < 0{\cdot}005$) (values expressed as mean ± 2 SD).*

cular posterior wall for the same groups of patients are summarised. Values of left ventricular posterior wall thickening were significantly higher ($P < 0{\cdot}005$) in asymmetric septal hypertrophy as compared with normals, whereas these values were significantly lower in patients with coronary artery disease and septal akinesia ($P < 0{\cdot}005$). Fig. 8 shows the normalised posterior wall velocity of $2{\cdot}6\ s^{-1}$ in a representative patient with genetic asymmetric septal hypertrophy. Fig. 9 shows the values for the normalised posterior wall velocity in the three patient groups studied.

Again values for left ventricular posterior wall normalised velocity were significantly higher in asymmetric septal hypertrophy ($P < 0{\cdot}005$), whereas no statistical significance has been found ($P < 0{\cdot}10$) between patients with coronary artery disease and normals.

The Table also shows that left ventricular internal dimensions in asymmetric septal hypertrophy both in diastole and systole were definitely smaller ($P < 0{\cdot}005$) than in the normal group, whereas in patients with coronary artery disease and septal akinesia these dimensions were higher than in normal individuals ($P < 0{\cdot}005$).

Discussion

Most patients with genetic asymmetric septal hypertrophy display a clinically observable rapid arterial pulse pressure rise corresponding to a rapid systolic pressure rise in the left ventricle and an increased ejection fraction. These observations suggest an overall left ventricular systolic function which is better than normal. However, echocardiographic analysis of septal contraction (Rossen *et al.*, 1974; Cohen *et al.*, 1975) and the morphological findings of cardiac muscle in this disease (Ferrans *et al.*, 1972) suggest that at least this part of the left ventricle has a reduced function. In this study, the mechanical behaviour of the left ventricle in genetic asymmetric septal hypertrophy was studied by analysis of the contraction patterns of the interventricular septum and left ventricular posterior wall, including the calculation of systolic thickening and the 'normalised' wall velocity. The results indicate that in genetic asymmetric septal hypertrophy the interventricular septum is indeed a hypocontractile structure with decreased values for

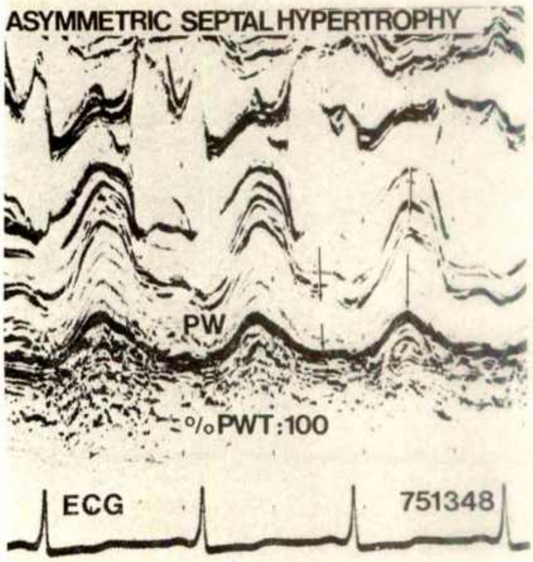

Fig. 6 *Representative example of the posterior wall dynamics in a patient with asymmetric septal hypertrophy. Systolic posterior wall thickening in this particular case is 100 per cent.*

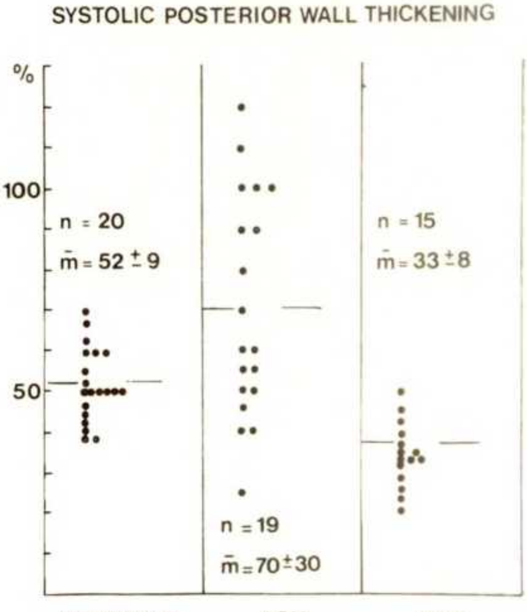

Fig. 7 *Systolic posterior wall thickening in 20 normal individuals is 52 ± 9 per cent, in 19 patients with asymmetric septal hypertrophy 70 ± 30 per cent, and in the 15 patients with coronary artery disease 33 ± 8 per cent. Systolic posterior wall thickening in normal individuals and in patients with coronary artery disease is significantly different from that seen in patients with asymmetric septal hypertrophy ($P < 0{\cdot}005$).*
Note that patients with asymmetric septal hypertrophy have a large range of systolic thickening (values expressed as mean ± 2SD).

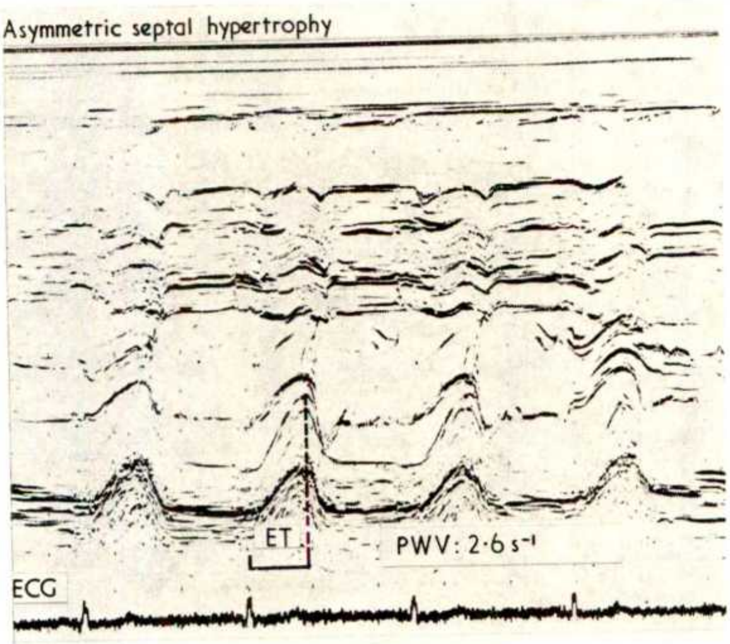

Fig. 8 *Representative example of normalised posterior wall velocity in a patient with asymmetric septal hypertrophy (ASH). Ejection time is calculated as the time from peak QRS to the point where the internal dimension of the left ventricle is smallest. 50 ms is subtracted from this value to account for the isovolumic phase (Cooper* et al., *1972). The value of normalised posterior wall velocity in this particular patient with asymmetric septal hypertrophy is* $2{\cdot}6\ s^{-1}$.

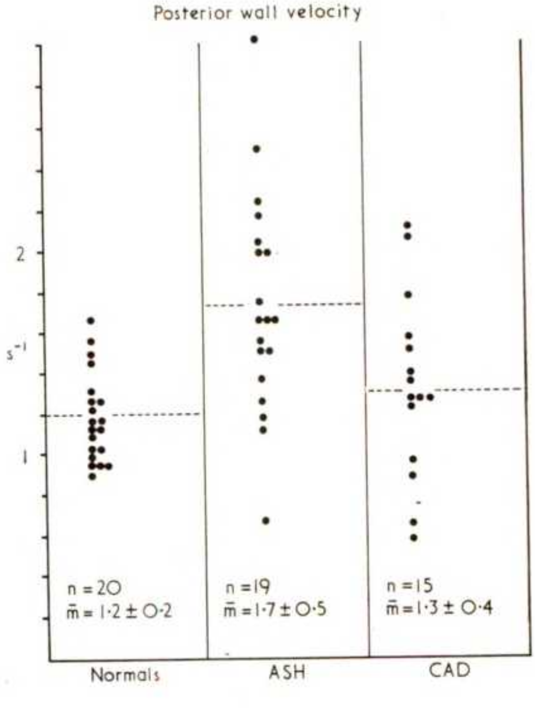

Fig. 9 *Normalised posterior wall velocity in 20 normal individuals was* $1{\cdot}2 \pm 0{\cdot}2\ s^{-1}$, *for 19 patients with asymmetric septal hypertrophy (ASH)* $1{\cdot}7 \pm 0{\cdot}5\ s^{-1}$, *and for 15 patients with coronary artery disease (CAD)* $1{\cdot}3 \pm 0{\cdot}4\ s^{-1}$. *Normalised posterior wall velocity is statistically significantly different for patients with asymmetric septal hypertrophy compared with normals* ($P < 0{\cdot}005$), *whereas this is not the case for patients with coronary artery disease* ($P < 0{\cdot}10$). *Note that in the three groups studied there is a broad range of values for normalised posterior wall velocity (values are expressed as mean ± 2SD).*

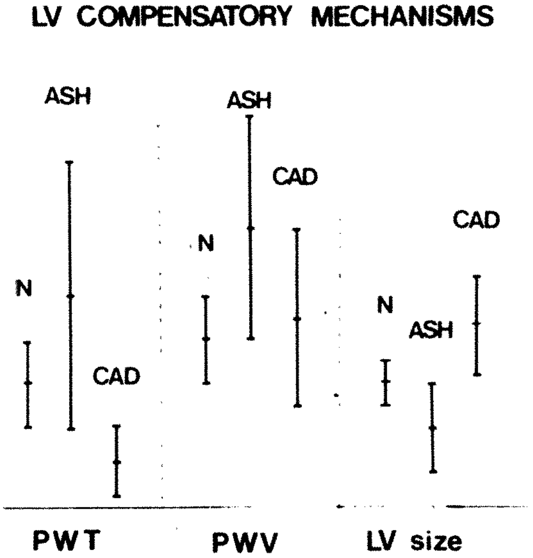

Fig. 10 *Left ventricular compensatory mechanisms in the three groups of individuals studied. Patients with asymmetric septal hypertrophy (ASH) compensate for the akinetic interventricular septum by a greater posterior wall thickening (PWT) and higher velocity of contraction of the posterior wall (PWV), whereas left ventricular size remains small, as compared with normal subjects. This is not true for patients who have coronary artery disease with septal akinesia. In these patients posterior wall thickening and velocity of contraction are not augmented, while left ventricular size is usually greater than normal.*

systolic thickening and that the left ventricular posterior wall tends to compensate for this effect. Indeed both systolic thickening and contraction velocity are higher than the corresponding indices measured from normal individuals. However, this is not the only mechanism that the left ventricle has available to maintain its overall systolic function, which becomes apparent when patients with coronary artery disease and septal akinesia are analysed. In those patients the left ventricular posterior wall percentage systolic thickening was uniformly decreased whereas the contraction velocity was normal. However, in these patients the left ventricular dimensions were larger than in the asymmetric septal hypertrophy group (Fig. 10). Thus it appears that the left ventricle has three different compensatory mechanisms in order to maintain its systolic function: (1) increase dimension (Starling mechanism); (2) increase systolic thickening, and (3) increase velocity of systolic contraction.

A review of the data reveals that the interventricular septum in genetic asymmetric septal hypertrophy is indeed a hypocontractile structure. Contractile function of left ventricular posterior wall as assessed from its systolic thickening and velocity is augmented or at least normal. Thus, the left ventricular mechanical behaviour in genetic asymmetric septal hypertrophy is mainly determined by normal or augmented left ventricular posterior wall contraction pattern while left ventricular size remains small. This is in contrast to findings in patients with coronary artery disease, where the left ventricular dimensions are increased while systolic thickening and normalised posterior wall velocity are usually decreased. These findings suggest that the left ventricle has at least three different compensatory mechanisms to maintain its systolic function as noted above.

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Sequence of retrograde atrial activation of the human heart[1]

Correlation with P wave polarity

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Studies were performed in 6 patients during open heart surgery to correlate the relative sequence of atrial activation with the polarity of the retrograde P wave in electrocardiographic leads II, III, and aVF. Bipolar atrial electrograms were recorded from selected sites during threshold pacing from sites low on the right side of the atrial septum which when paced resulted in the inscription of either negative or positive P waves in electrocardiograph leads II, III, and aVF. When the atria were paced from a site just anterior to the coronary sinus ostium (negative P waves), the posteroinferior left atrium was activated early and Bachmann's bundle late during the inscription of the P wave. When the atria were paced from a site 2 cm anterior to the coronary sinus ostial site (positive P waves), Bachmann's bundle was activated early during the P wave and the posteroinferior left atrium was activated relatively later. These data from man are consistent with previous studies in the canine heart. Therefore, we deduced that in man during the inscription of negative retrograde P waves in leads II, III, and aVF, atrial activation occurs primarily in a retrograde fashion. However, during the inscription of positive retrograde P waves in man, activation occurs rapidly up the interatrial septum (we believe via the anterior internodal pathway) to Bachmann's bundle, from where it then spreads in a manner similar to that which occurs during normal sinus rhythm.

It previously has been shown both in the experimental animal (Scherf and Shookhoff, 1925; Borman and Meek, 1931; Brumlík, 1958; Moore *et al.*, 1967, 1971; Waldo *et al.*, 1971, 1975) and in man (Daniélopolu and Proca, 1926; Gallavardin and Veil, 1928; McGuire and Rosenberger, 1931; Dressler and Roesler, 1956; Latour and Puech, 1957; Gonzalez Videla, 1968; Waldo *et al.*, 1968, 1970) that retrograde activation of the atria may result in the inscription of positive and biphasic (−, +) as well as negative P waves in electrocardiographic leads II, III, and aVF. Detailed studies of the sequence of activation in canine atria (Waldo *et al.*, 1975) showed that when the retrograde P wave was negative, the atria were activated primarily in a retrograde fashion. However, when the retrograde P wave was positive in those same leads, activation of the atria was such that the wave of excitation travelled rapidly up the interatrial septum to Bachmann's bundle from which point it spread inferiorly over a significant portion of both atria in a manner similar to that which occurred during sinus rhythm. The time of arrival of the impulse at Bachmann's bundle relative to its arrival at the posteroinferior left atrium was critical in determining the polarity and morphology of the P wave. Positive retrograde P waves were associated with early activation of Bachmann's bundle and later activation of the posteroinferior left atrium. Negative retrograde P waves were associated with relatively early activation of the posteroinferior left atrium and later activation of Bachmann's bundle. Thus, the relative activation times at Bachmann's bundle and the posteroinferior left atrium provide markers for understanding the sequence of atrial activation. The present study was conducted to determine if these experimental observations in the dog hold true for man as well.

It has been shown earlier that when the human atria from the region of the coronary sinus ostium

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are paced, negative P waves or negative P waves with a small late positive component in electrocardiographic leads II, III, and aVF are produced (Waldo *et al.*, 1970). When the atria are paced from sites in the AV junction increasingly more anterior relative to the coronary sinus ostium, biphasic (−, +) and finally frankly positive P waves in leads II, III, and aVF are produced (Waldo *et al.*, 1970). In the present study in patients, the atria were paced from two AV junctional sites, one from which pacing produced negative retrograde P waves and the other from which pacing produced positive retrograde P waves in leads II, III, and aVF. The relative sequence of atrial activation during inscription of these P waves was then studied and compared with previous observations in the canine heart.

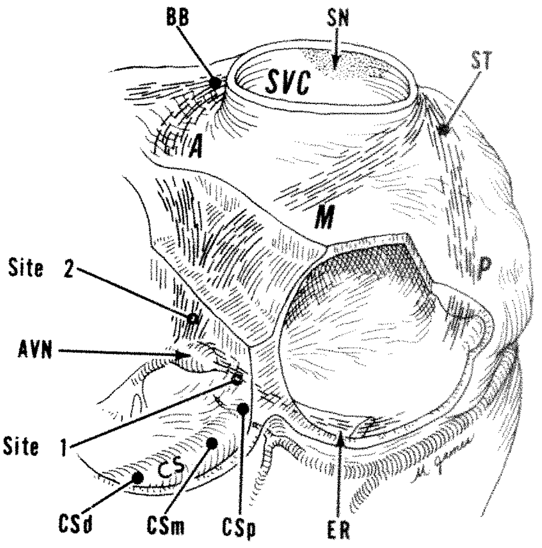

Fig. 1 *This drawing is a partial view of the heart from above and behind the left atrium with parts of the right atrium and interatrial septum cut away. The black dots in the coronary sinus (CS) indicate the distal (CSd), middle (CSm), and proximal (CSp) coronary sinus catheter electrode recording sites. The CSd and CSm sites record activation from the posteroinferior left atrium. Other black dots indicate Bachmann's bundle (BB) and sulcus terminalis (ST) electrode recording sites. The anterior (A), middle (M), and posterior (P) internodal pathways and the interatrial pathway which courses through Bachmann's bundle are schematically depicted sweeps of broken lines. The relation of pacing sites (open circles) 1 and 2 to the internodal pathways is clearly shown. Additional abbreviations: AVN = atrioventricular node; SN = sinus node; SVC = superior vena cava; ER = Eustachian ridge.*

Methods

Using previously reported intraoperative cardiac electrophysiological techniques (Waldo *et al.*, 1968, 1970, 1973), 6 patients between 8 and 56 years of age were studied during open heart surgery. Five patients had secundum atrial septal defects and one patient had a primum atrial septal defect. No patient had any conduction abnormality in the electrocardiogram before or after the open heart surgery. Observations were made in each case at normothermia during cardiopulmonary bypass after the repair of the atrial septal defect. For each patient, bipolar electrograms were recorded from Bachmann's bundle at a point overlying the interatrial septum, from the sulcus terminalis at a point just below the sinus node, from just within the coronary sinus ostium, and from posteroinferior left atrial sites (Fig. 1 and 2). Electrograms from the sulcus terminalis site (ST) were recorded in all 6 patients from a plaque electrode (Waldo *et al.*, 1968, 1970) sewn there before cardiopulmonary bypass. Electrograms from the Bachmann's bundle site (BB) were recorded from a plaque electrode sewn there before cardiopulmonary bypass in 4 patients, and from a catheter electrode sutured securely before cardiopulmonary bypass to hold the electrode at this site in 2 patients. Electrograms were recorded from the coronary sinus ostium and the posteroinferior left atrial sites in 5 patients by inserting a multipolar catheter electrode into the coronary sinus ostium; the most proximal electrode pair (CSp) was located just within the coronary sinus ostium, a second electrode pair (CSm) was 1·0 cm distal to the proximal pair, and a third electrode pair (CSd) was 1·8 cm distal to the middle electrode pair. The interelectrode distance for each pair of electrodes was 2 mm. This multipolar electrode catheter was placed in the coronary sinus during cardiopulmonary bypass via the atriotomy in the free wall of the right atrium created for the repair of the atrial septal defect. It has been shown earlier that this type of atriotomy does not affect P wave polarity or morphology when pacing from low atrial septal sites (Waldo *et al.*, 1970). In one patient, the multipolar catheter electrode was placed epicardially to record from the posteroinferior left atrial sites by positioning the catheter just superior to the course of the coronary sinus and directly below the inferior pulmonary veins. The catheter was quite stable in this position as it was sandwiched securely between the pericardium and the heart. In this position the most proximal electrode pair was located on the epicardium just posterior to the inferior vena cava, such that the CSp site using this

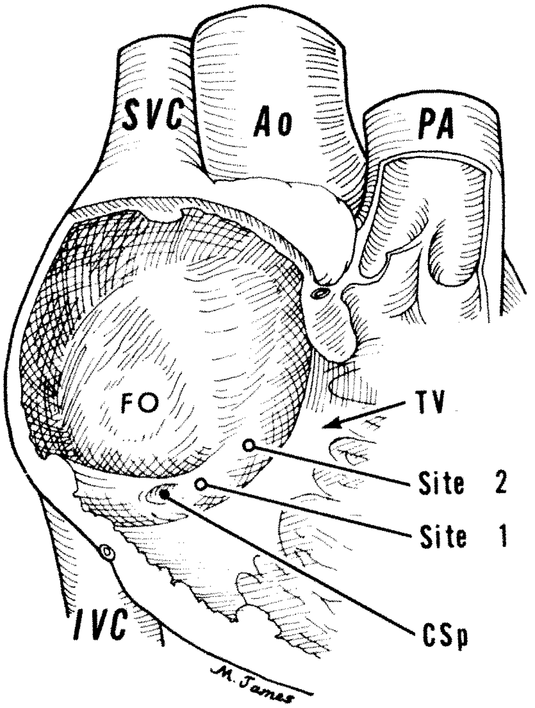

Fig. 2 *In this drawing, the free walls of the right atrium and right ventricle have been removed. Pacing site 1 is just anterior to the coronary sinus ostium and pacing site 2 is 2 cm anterior to pacing site 1. The proximal coronary sinus electrode site (CSp) is represented by the black dot which lies just within the coronary sinus ostium. Additional abbreviations: Ao = aorta; PA = pulmonary artery; SVC = superior vena cava; IVC = inferior vena cava; TV = tricuspid valve; FO = fossa ovalis.*

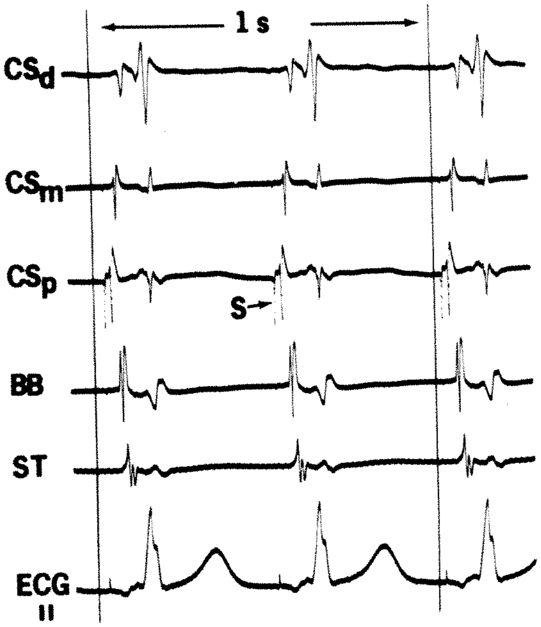

Fig. 3 *Electrocardiograph lead II recorded from one patient simultaneously with electrograms from the five standard recording sites during a rhythm in which the atria are paced from site 1. S = stimulus artefact. See text for discussion.*

technique approximated the CSm site using the technique in which the catheter electrode was inserted into the coronary sinus. Similarly, with the epicardial placement of the catheter electrode, the CSm and CSd epicardial sites were correspondingly more distal relative to the coronary sinus ostium than those sites for the catheter electrode placed within the coronary sinus.

For each study the atria were paced with bipolar threshold stimuli delivered through a hand-held electrode probe from two sites low in the right atrial septum (Fig. 1 and 2). One site (No. 1) just anterior to the coronary sinus ostium was selected because pacing from this site produced P waves which were either entirely negative or negative with a very small late positive component in leads II, III, and aVF (Waldo *et al.*, 1970). The other site (No. 2), about 2·0 cm anterior to the coronary sinus ostium, was selected because pacing from this site produced positive P waves in leads II, III, and aVF (Waldo *et al.*, 1970). The rate at which the atria were paced was just fast enough to achieve stable atrial capture, and generally was 10 beats/min faster than the spontaneous rate.

Results

The results were consistent in all patients. Table 1 contains the conduction times to selected recording sites during atrial pacing. Case 6 had an ostium primum atrial septal defect and thus we could pace only from site 1 (Waldo *et al.*, 1973). Data from two representative studies in which a plaque electrode was sewn to the Bachmann's bundle site and in which the multipolar electrode was inserted into the coronary sinus will be shown.

Fig. 3 illustrates the records from case 5 when site 1 just anterior to the coronary sinus ostium was paced. The P wave in lead II was primarily negative with a small late positive component (Waldo *et al.*, 1970). Conduction time to the proximal coronary sinus electrode site was 21 ms, Table *Conduction times (ms) to selected recording sites*

Case No.	*Pacing site*	*BB*	*CSp*	*CSm*	*CSd*
1	1	87	29	40	56
	2	45	104	120	104
2	1	58	—	51	72
	2	43	62	81	90
3	1	63	—	16	33
	2	30	34	50	73
4	1	87	13	39	62
	2	68	73	99	123
5	1	45	21	37	60
	2	25	29	43	69
6	1	48	—	14	25
	2	—	—	—	—

to the middle coronary sinus electrode site 37 ms, to the Bachmann's bundle site 45 ms, and to the distal coronary sinus and sulcus terminalis sites 60 ms each. When in the same patient the atria were paced from the low atrial septal site 2 cm anterior to the coronary sinus ostium (site 2), a positive P wave was inscribed in leads II, III, and aVF (Fig. 4). Conduction time to the Bachmann's bundle site then was 25 ms, i.e. 20 ms shorter than when the other site was paced. Conduction time to the proximal coronary sinus electrode site was 29 ms, i.e. this site was activated after the Bachmann's bundle site. Furthermore, both sites were activated before the onset of the inscription of the P wave in leads II, III, and aVF. Conduction time to the middle coronary sinus electrode site was 43 ms or 18 ms longer than to the Bachmann's bundle site. Conduction time to the sulcus terminalis site was 43 ms.

Fig. 5 and 6 illustrate records from case 3. Pacing from site 1 just anterior to the coronary sinus ostium again resulted in negative P waves in leads II, III, and aVF. The electrode probe used to pace the atria was actually in contact with the proximal coronary sinus electrode, which explains the movement artefact in the electrogram recorded from the proximal coronary sinus site. Parenthetically, this occurred also in cases 2 and 6 (Table). Conduction time to the middle coronary sinus electrode site was 16 ms and to the distal coronary sinus site 33 ms. By using the left time line as reference, it is clear that the conduction time to the Bachmann's bundle site (63 ms) was much longer than that to the

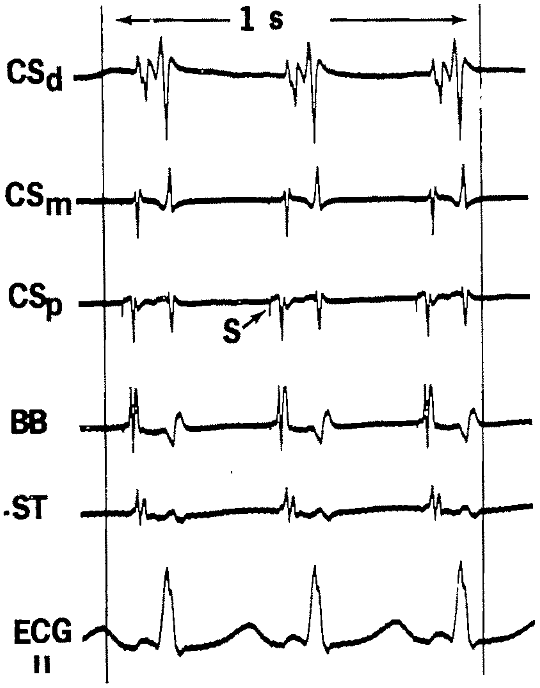

Fig. 4 *Electrocardiogram lead II recorded simultaneously with the atrial electrogram from the five standard recording sites during a rhythm in which the atria are paced from site 2 (same patient as in Fig. 3). See text for discussion.*

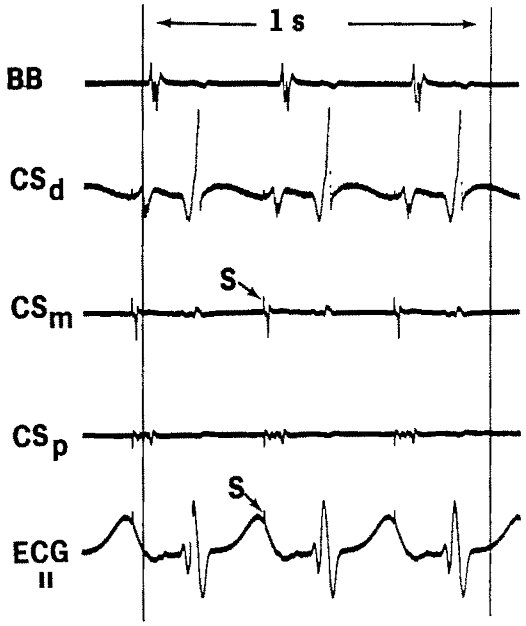

Fig. 5 *Electrocardiogram lead II recorded from a second patient simultaneously with four atrial electrograms (Bachmann's bundle and the three coronary sinus sites) during a rhythm in which the atria are paced from site 1. See text for discussion.*

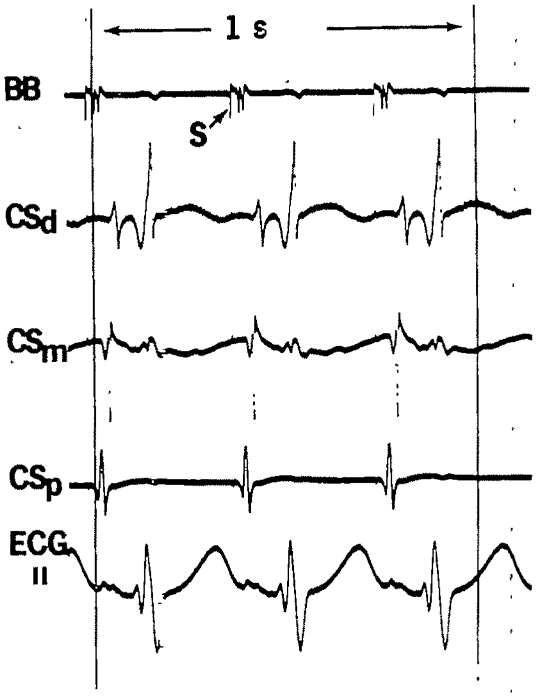

Fig. 6 *Electrocardiogram lead II recorded simultaneously with the same atrial electrograms recorded from the four sites as in Fig. 5 (same patient) during a rhythm in which the atria are paced from site 2. See text for discussion.*

coronary sinus sites. Also, activation of the Bachmann's bundle site was quite late relative to the inscription of the P wave. When in the same patient the atria were paced from the low atrial septal site 2 cm anterior to the coronary sinus ostium (site 2), the P waves in leads II, III, and aVF were positive. Conduction time to the Bachmann's bundle site was then only 30 ms, and again, by using the time line on the left as reference, it can be seen that this site was activated distinctly before inscription of the P wave (Fig. 6). Conduction time to the most proximal site in the coronary sinus was 34 ms or longer than to the Bachmann's bundle site. Conduction time to the middle coronary sinus site was 50 ms and to the distal coronary sinus electrode site 73 ms.

In cases 1 and 4, the stimulus-to-onset of the inscription of the P wave (SP) interval when pacing from site 2 was 40 ms and 48 ms, respectively. When pacing the atria, an SP interval is normally present, though this interval in these two patients is in the upper range of the previously observed stimulus-to-P intervals (Waldo *et al.*, 1970; MacLean *et al.*, 1975). We believe that this in part explains the relatively long conduction times to the selected recording sites (Table). In addition, an interesting finding in case 1 was that the CSd site was activated before the CSm site and virtually simultaneously with the CSp site when pacing from site 2 (Table). Case 1 was the only patient in whom the CS sites were recorded with the epicardially placed catheter electrode. We believe that the distal electrode pair (CSd) probably was located somewhat superiorly to the CSd site recorded from in the other patients and with the inscription of a positive retrograde P wave, this site very likely was activated by a wave-front coming down from above (as we would predict) rather than from a retrograde wave-front coming up from below. When pacing from site 1 in case 1, during the inscription of negative retrograde P waves, the CSd site was activated later than both the CSp and CSm sites, very likely by a retrograde wave-front (as we would predict). Thus, the conduction times to the selected atrial recording sites in this patient as well as the other 5 patients are well explained by our hypothesis regarding the sequence of atrial activation during the inscription of either positive or negative retrograde P waves.

Discussion

COMPARISON OF RETROGRADE ACTIVATION IN HUMAN AND CANINE HEART

The relative sequence of atrial activation during atrial pacing from low atrial septal sites which results in either negative or positive P waves in leads II, III, and aVF in man is similar to that shown in previous experimental studies in the dog (Moore *et al.*, 1971; Waldo *et al.*, 1971, 1975). Since the relative sequence of atrial activation during the inscription of retrograde P waves has been correlated with the actual sequence of activation of both the entire right and left atrium for the canine atria and since the relative sequence of atrial activation during the inscription of these P waves is the same for man as for the canine heart, it is logical to make certain assumptions about the actual sequence of atrial activation in the human heart. When negative retrograde P waves are produced in leads II, III, and aVF, the early arrival of the impulse low in the left atrium and its later arrival at Bachmann's bundle reflects a retrograde sequence of activation within the two atria. Similarly, when positive retrograde P waves are produced in II, III, and aVF, then the arrival of the impulse at Bachmann's bundle earlier than at low left atrial sites reflects the rapid retrograde spread of the impulse up the interatrial septum to Bachmann's bundle, which we believe occurs via the anterior internodal pathway (Fig. 1). From Bachmann's bundle the impulse then spreads to depolarise significant portions of both atria in a manner similar to that which occurs during spontaneous sinus rhythm.

This interpretation of atrial activation in man not only fits the present data but also fits with previous studies of retrograde P wave polarity in man. If the retrograde positive P waves depends, as we have stated, on rapid retrograde spread of the impulse up the interatrial septum to Bachmann's bundle, then the lesion in patients with ostium primum atrial septal defects should preclude this from occurring and no positive retrograde P wave should be possible in these patients. This, in fact, was shown by a previous study (Waldo *et al.*, 1975) as well as the present study in which low atrial septal sites were paced in patients with ostium primum atrial septal defects and only negative retrograde P waves in leads II, III, and aVF were produced. In contrast, as shown by a previous study (Waldo *et al.*, 1970) as well as the present study in patients with ostium secundum or sinus venosus atrial septal defects or with an intact atrial septum, i.e. patients in whom the main route of conduction in the interatrial septum is intact, positive as well as negative retrograde P waves were produced when low atrial septal sites were paced.

'RETROGRADE' POSITIVE P WAVES

The term 'retrograde' positive P waves may seem a semantic contradiction by usual electrocardiographic concepts. However, it is clear that positive P waves in leads II, III, and aVF can occur in man during activation of the atria from low atrial sites, and during such pacing at least the initial spread of atrial activation necessarily is retrograde. Therefore, it seems reasonable to use this term, particularly as it emphasises the difference between it and retrograde negative P waves.

Since there are so few reported cases of positive retrograde P waves during spontaneous ectopic rhythms (Daniélopolu and Proca, 1926; Gallavardin and Veil, 1928; McGuire and Rosenberger, 1931; Dressler and Roesler, 1956; Latour and Puech, 1957; Gonzalez Videla, 1968), one may ask whether such P waves are anything more than a rare curiosity. It has been long and widely believed that retrograde activation of the atria necessarily results in negative P waves in leads II, III, and aVF (Lewis, 1921), but our results suggest that one also must consider the possibility that an ectopic rhythm with positive P waves in II, III, and aVF could represent 'retrograde' activation of the atria. There is evidence to suggest that such spontaneous rhythms are possible. For example, the low atrial septal sites which when paced result in retrograde positive P waves in II, III, and aVF are in close proximity to the internodal pathways (James, 1963; Merideth and Titus, 1968). Since specialised cells in these pathways have been shown to be capable of spontaneous impulse formation (Hogan and Davis, 1968), then ectopic rhythms which may be initiated from such a site could be expected to produce positive retrograde P waves. The rhythm formerly known as coronary nodal rhythm may be one example, since it is associated with positive P waves in leads II, III, and aVF and with a short PR interval (Langendorf *et al.*, 1944; Brumlík, 1958; Waldo *et al.*, 1970). In a classic review of paroxysmal atrial tachycardia (Barker *et al.*, 1943), fully one-third of these rhythms were said to have positive P waves in II, III, and aVF. Since that time, it has become generally accepted that paroxysmal atrial tachycardia is an AV nodal re-entrant rhythm (Goldreyer and Bigger, 1971). Depending upon the emergence and propagation of atrial septal activation, some of these re-entrant rhythms could be expected to have positive P waves in II, III, and aVF.

Although it is very likely true that there are spontaneously occurring sinus node re-entrant rhythms, possibly including some of the rhythms described above (Barker *et al.*, 1943), all the suggested criteria (Narula, 1974) for the diagnosis of this rhythm (positive P waves in leads II, III, and aVF similar to the P waves which occur during sinus rhythm, and a relative sequence of atrial activation such that a site high in the right atrium is activated before a site low in the right atrium) were fulfilled in the present study when we paced the atria from the low atrial septum (site 2). While our observations do not disprove the concept of sinus node re-entrant rhythms, nor is it our intent to suggest that sinus node re-entrant rhythms do not occur, it is clear that the criteria so far proposed for the diagnosis of such rhythms also are fulfilled by rhythms originating low in the atrial septum (our site 2). To know with certainty the site of origin for re-entrant supraventricular arrhythmias having positive P waves in leads II, III, and aVF, additional criteria will have to be established.

SPECIALISED ATRIAL CONDUCTION

During the inscription of retrograde positive P waves in II, III, and aVF, the spread of activation up the interatrial septum in these human atria was so rapid that the Bachmann's bundle site was depolarised before the proximal coronary sinus site (CSp), i.e. the site just within the coronary sinus ostium and also usually before the inscription of the P wave. Since the distance from site 2 to the

Bachmann's bundle site is more than twice as long as the distance from site 2 to the CSp site (Fig. 1), we believe these data further support the accumulated evidence summarised recently (MacLean *et al.*, 1974) favouring functionally important specialised atrial pathways in both human and canine hearts.

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Heart rate response to Valsalva manoeuvre
Reproducibility in normals, and relation to variation in resting heart rate in diabetics

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The reproducibility of the heart rate response to the Valsalva manoeuvre was assessed in 12 young normal subjects who each repeated the manoeuvre 10 times. The length of the RR intervals before, during, and after each Valsalva manoeuvre was measured from an electrocardiogram and the changes expressed as two ratios: the 'tachycardia' ratio and the 'Valsalva' ratio. The within-subject variation was ±0·044 for the tachycardia ratio and ±0·18 for the Valsalva ratio, while the between-subject variation was 0·10 for the tachycardia ratio and 0·37 for the Valsalva ratio. The heart rate response to the Valsalva manoeuvre was also found to be reproducible in 7 older normal subjects.

In 100 diabetic subjects with varying degrees of autonomic neuropathy, the heart rate response to the Valsalva manoeuvre was compared with the heart rate variation from a resting electrocardiogram. The heart rate variation correlated significantly with both the tachycardia ratio ($r=0{\cdot}727$, $P<0{\cdot}001$) and the Valsalva ratio ($r=0{\cdot}659$, $P<0{\cdot}001$).

Thus, the heart rate response to the Valsalva manoeuvre is reproducible in normal subjects, and in diabetics, heart rate variation can simply be used as a test of autonomic function when more sophisticated tests are not available.

The Valsalva manoeuvre, named after Antonio Maria Valsalva (1666–1723), is widely regarded as a simple method of evaluating baroreflex integrity. Despite its use in many clinical and experimental situations, only limited studies of its reproducibility have been carried out (Levin, 1966). Changes in intra-arterial blood pressure have been used to assess the response to the Valsalva manoeuvre, but heart rate changes have also been shown to be reliable (Elisberg, 1963) and have the advantage of being noninvasive.

A further test of autonomic function has recently been proposed by Wheeler and Watkins (1973) in which the variation in resting heart rate was measured with a heart rate meter. The aim of the present study was first to define the reproducibility of the heart rate response to the Valsalva manoeuvre in normal subjects and secondly to see whether, in a group of patients with diabetes, measurements from a resting electrocardiogram of heart rate variation could reliably be used as a test of autonomic function.

Subjects and methods

Three groups of subjects were studied: the first group consisted of 12 normal, fit young subjects (8 men and 4 women, aged 20 to 41 years); the second 7 normal older subjects (3 men and 4 women, aged 52 to 66 years); and the third 100 diabetics, some of whom had definite autonomic neuropathy, some had impotence alone, while the remainder had no symptoms referable to the autonomic nervous system.

In each young normal subject the Valsalva manoeuvre was repeated at different times of the day on 10 occasions over a 2-month period. In each older normal subject the Valsalva manoeuvre was repeated 5 times over a one-week period. The 100 diabetics performed the manoeuvre on one occasion only.

Each subject performed a Valsalva manoeuvre by blowing through a mouthpiece attached to a manometer and maintaining a pressure of 40 mmHg for 15 seconds. Care was taken that the subject was not blowing with his cheeks, and had an open glottis (a true Valsalva was clinically confirmed by a florid face and distension of the neck veins, and by a characteristic 'gasp' on release). Once the technique

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had been mastered the test was performed 3 times and the mean values used in calculating the results. Heart rate was measured from an electrocardiogram recorded continuously from one minute before until one minute after each manoeuvre. The subjects remained seated throughout and rested for at least 2 minutes between each Valsalva manoeuvre.

The longest and shortest RR intervals were measured from the electrocardiogram before, during, and after the Valsalva manoeuvre and the following calculations were made.

(1) Mean resting heart rate (mean of longest and shortest RR interval before the manoeuvre).
(2) Variation in resting heart rate (difference between longest and shortest RR interval before the manoeuvre).
(3) Tachycardia ratio (shortest RR interval during the manoeuvre divided by the longest RR interval before).
(4) Valsalva ratio (longest RR interval after the manoeuvre, divided by the shortest RR interval during it).

Results

REPRODUCIBILITY IN YOUNG NORMAL SUBJECTS

Table 1 summarises the findings in the young normal subjects. There were no statistically significant differences between the grouped data of the males and females: all the results have therefore been analysed together. Within-subject and between-subject variation was calculated by standard analysis of variance (Armitage, 1971). The within-subject variation for the group (expressed as the standard deviation of repeated measurements within each individual) was 0·044 for the tachycardia ratio and 0·18 for the Valsalva ratio. The between-subject variation for the group (expressed as the standard deviation of the mean values of all individuals) was 0·10 for the tachycardia ratio and 0·37 for the Valsalva ratio.

Interpretation of differences in successive observations in the same subject is often difficult in clinical practice. For normal individuals more than 95 per cent of successive readings would differ by less than 0·12 for the tachycardia ratio, and 0·51 for the Valsalva ratio. This is calculated from the formula $2\times\sqrt{2}\times \mathrm{SD}$, since the variance of differences in successive observations is twice the variance of individual observations (Armitage, 1971).

REPRODUCIBILITY IN OLDER NORMAL SUBJECTS

Table 2 shows the results in the older normal subjects. The mean resting heart rate and the mean tachycardia ratio in the older group were similar to the younger group, but the mean individual variation in resting heart rate and the mean Valsalva ratio were both lower in the older group, the differences just reaching statistical significance ($P < 0{\cdot}05$). There were no statistically significant differences between the younger and older groups in their within-subject variation (0·043 for the tachycardia ratio and 0·17 for the Valsalva ratio). The between-subject variation was 0·05 for the tachycardia ratio and 0·18 for the Valsalva ratio.

COMPARISON OF VALSALVA MANOEUVRE WITH VARIATION IN RESTING HEART RATE IN DIABETICS

The tachycardia ratio and the Valsalva ratio in the 100 diabetics are shown in Fig. 1. Fig. 2 and 3 show the relation between the individual variation in resting heart rate and the tachycardia ratio (Fig. 2) and the Valsalva ratio (Fig. 3). After the influence of both age and the resting heart rate had been eliminated, using a partial correlation coefficient technique, there was close relation between the variation in resting heart rate and both the tachycardia ratio ($r=0{\cdot}727$, $P < 0{\cdot}001$) and the Valsalva ratio ($r=0{\cdot}659$, $P < 0{\cdot}001$) in the group as a whole.

Table 1 *Heart rate responses to the Valsalva manoeuvre in 12 young normal subjects*

Subject	*Age (y)*	*Sex*	*Resting RR interval (ms)*	*Variation in resting RR interval (ms)*	*Tachycardia ratio**	*Valsalva ratio**
1	23	M	733 ±77	136 ±59	0·61 ±0·05	2·24 ±0·14
2	34	M	781 ±23	117 ±38	0·68 ±0·03	1·99 ±0·10
3	31	M	831 ±44	77 ±15	0·73 ±0·03	1·47 ±0·06
4	22	M	855 ±81	161 ±53	0·60 ±0·05	2·09 ±0·19
5	41	M	736 ±64	133 ±66	0·57 ±0·03	2·48 ±0·31
6	30	M	775 ±83	193 ±60	0·90 ±0·04	1·22 ±0·13
7	29	M	990 ±58	277 ±105	0·60 ±0·05	1·77 ±0·18
8	28	M	681 ±51	51 ±17	0·80 ±0·04	1·38 ±0·17
9	22	F	724 ±41	124 ±51	0·69 ±0·05	1·92 ±0·15
10	32	F	746 ±54	87 ±59	0·73 ±0·05	1·58 ±0·22
11	20	F	592 ±42	91 ±29	0·74 ±0·07	1·81 ±0·18
12	22	F	850 ±58	220 ±36	0·56 ±0·03	2·06 ±0·24
Mean			774 ±100	139 ±65	0·68 ±0·10	1·83 ±0·37

*Mean of 10 observations (±SD).

Table 2 *Heart rate responses to the Valsalva manoeuvre in 7 older normal subjects*

Subject	*Age (y)*	*Sex*	*Resting RR interval (ms)*	*Variation in resting RR interval (ms)*	*Tachycardia ratio**	*Valsalva ratio**
13	66	F	800 ±56	68 ±24	0·84 ±0·06	1·28 ±0·15
14	55	F	884 ±44	148 ±60	0·71 ±0·06	1·49 ±0·16
15	52	F	832 ±44	72 ±28	0·73 ±0·04	1·33 ±0·08
16	56	M	772 ±72	76 ±12	0·74 ±0·03	1·80 ±0·14
17	52	M	800 ±80	88 ±40	0·70 ±0·02	1·63 ±0·08
18	65	M	884 ±80	92 ±24	0·74 ±0·05	1·43 ±0·14
19	57	F	688 ±60	56 ±16	0·77 ±0·04	1·46 ±0·11
Mean	58	—	809 ±68	86 ±30	0·75 ±0·05	1·49 ±0·18

*Mean of 5 observations (±SD).

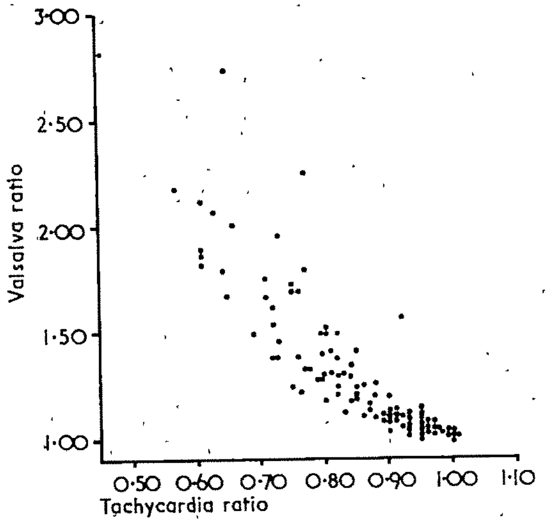

Fig. 1 *The tachycardia and Valsalva ratios in 100 diabetics.*

Thus, in these 100 diabetics, some of whom had varying degrees of autonomic neuropathy, as determined by an abnormal Valsalva ratio, the variation in resting heart rate was significantly correlated with the results of the Valsalva manoeuvre.

Discussion

The heart rate response to the Valsalva manoeuvre has often been used to assess cardiac autonomic integrity in diabetes (Nathanielsz and Ross, 1967; Bishnu and Berenyi, 1971; Ewing *et al.*, 1973; Low *et al.*, 1975). In common with other noninvasive methods it has the obvious advantage of being simple, and provided it can be shown to be reproducible, can be used in serial studies as an outpatient procedure. In the only previous observations on the reproducibility of the heart rate response to the Valsalva manoeuvre, Levin (1966) found a difference of less than 10 per cent when observations were re-

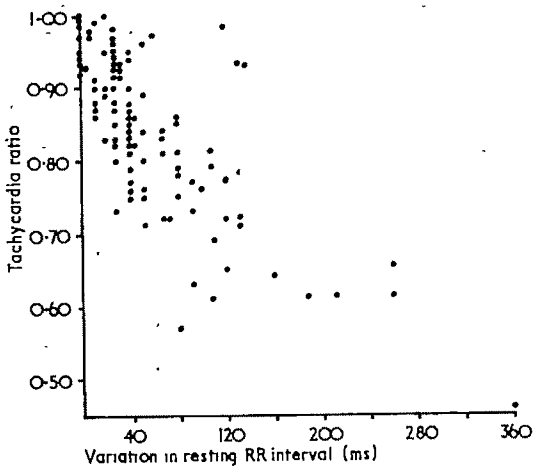

Fig. 2 *The relation between the variation in resting RR interval and the tachycardia ratio in 100 diabetics.*

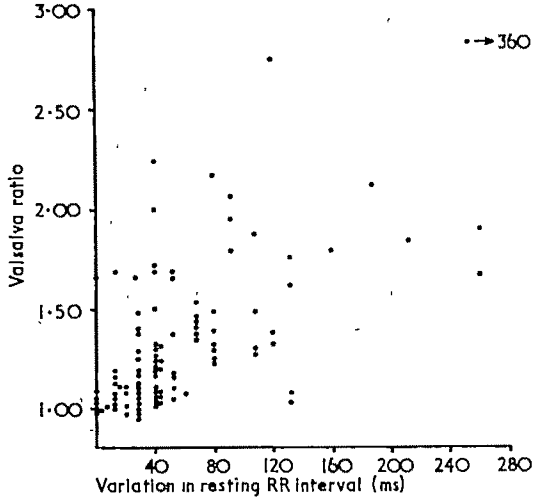

Fig. 3 *The relation between the variation in resting RR interval and the Valsalva ratio in 100 diabetics.*

peated after one week; this appears to be a close correlation, but only 2 determinations were made. In the present study we repeated the Valsalva manoeuvre 10 times over a 2-month period in the younger normal subjects and the results show that the heart rate response is indeed reproducible on repeated occasions. This reproducibility can be compared favourably with results obtained using other invasive and noninvasive techniques. It is now possible, within the limits that we have defined, to know whether variations in the response of individuals on repeated occasions are the result of normal variability or of pathological processes. To provide a more valid comparison with the older diabetics, 7 further normal subjects, all over 50 years, repeated the Valsalva manoeuvre 5 times. The reproducibility was slightly better than in the younger normal group, but this may be explained by the shorter period (one week) over which the measurements were made. It is also apparent from these results that variation in heart rate falls slightly with age, as does the Valsalva ratio.

The blood pressure has previously been regarded as the standard method for interpreting the response to the Valsalva manoeuvre though intra-arterial cannulation is required. Recently, however, the method of characterising a Valsalva manoeuvre as normal or abnormal by the relation between the percentage increase in diastolic blood pressure and the percentage decrease in pulse pressure during the Valsalva manoeuvre has been shown to be less reliable than originally thought (Johnson and Spalding, 1974). Both Elisberg (1963) and Levin (1966) have shown that the heart rate changes are a reliable indicator of haemodynamic events during and after the strain of the Valsalva manoeuvre. Levin coined the term 'Valsalva ratio', but as can be seen from the study, the 'tachycardia ratio' is closely related to it. Though the tachycardia ratio shows less variation when an individual repeats the Valsalva manoeuvre and therefore appears to be a better index, in practice the Valsalva ratio has the advantage of being independent of the resting heart rate. It has, therefore, been preferred by most investigators.

Heart rate variation measured by either a heart rate meter (Wheeler and Watkins, 1973) or an arrhythmia computer (Murray *et al.*, 1975) has been shown to be abnormal in some diabetics, and is the result of damage to the vagus nerve (Wheeler and Watkins, 1973). In another recent paper (Lloyd-Mostyn and Watkins, 1975), diabetics with clinical autonomic neuropathy were subjected to a variety of tests, and found to have both abnormal heart rate variation and abnormal responses to the Valsalva manoeuvre. Details of the responses were not, however, given. The diabetics in our study included those with definite autonomic neuropathy, those with impotence alone, and a group of patients without any symptoms referable to the autonomic nervous system. We thus had a spectrum of diabetics from those with a normal response to the Valsalva manoeuvre to those with no heart rate response at all. It can be seen from Fig. 2 and 3 that a simple measurement of the heart rate variation on the electrocardiogram correlated closely with the Valsalva responses in the group as a whole. Furthermore, only 2 subjects with a Valsalva ratio of 1·20 or less, which we have previously defined as abnormal or borderline (Ewing *et al.* 1973), had a heart rate variation on the resting electrocardiogram of more than 65 ms. Measurement of the longest and shortest RR intervals from a resting electrocardiogram can thus be used as a simple though not diagnostic screening test for autonomic neuropathy when more sophisticated facilities are not readily available.

We thank Dr. R. J. Prescott for his advice and help in the statistical analysis.

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Clinical significance of multiple systolic clicks from Starr-Edwards prosthetic aortic valves

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The use of echocardiography, phonocardiography, and spectroanalysis has enhanced the ability to detect prosthetic valve dysfunction even before the onset of symptoms in many patients. Reduction in the intensity of the opening and closing clicks and the appearance of new murmurs have been the most frequently reported observations in predicting prosthetic valve dysfunction. Simultaneous echocardiography, phonocardiography, and spectroanalysis were performed on 31 patients with Starr-Edwards prosthetic aortic valves. Eighteen patients had valves with metal (titanium or 'stellite') poppets, and 13 had valves with non-metal (silastic) poppets. In all patients with normally functioning valves with metal poppets, there were multiple systolic clicks on auscultation and confirmed by phonocardiography and spectroanalysis. In none of the patients with non-metal poppets were there clicks other than those associated with the normal opening and closing movements of the poppets. Three of the 18 patients with metal poppets did not manifest multiple systolic clicks, yet the cut-off frequencies on spectroanalysis for opening and closing clicks in 1 of these patients were normal. Prosthetic valve dysfunction was shown in all 3 patients by cardiac catheterisation or at operation. We conclude that multiple systolic clicks are normal for patients with Starr-Edwards prosthetic aortic valves with metal (titanium or 'stellite') poppets, and that the absence of multiple systolic clicks may indicate prosthetic valve dysfunction even when the cut-off frequencies of the opening and closing clicks are normal.

Because of the large number and different types of prosthetic valves, it is essential that the clinician be familiar with the normal characteristics of each type. Spectroanalysis is a fairly new technique used to complement the information obtained by echocardiographic and phonocardiographic examination (Winters *et al.*, 1967; Hylen *et al.*, 1969; Waxler *et al.*, 1973; Gordon *et al.*, 1974). This paper compares two types of Starr-Edwards prosthetic aortic valves—one with a metal (titanium or 'stellite') poppet and one with a non-metal (silastic) poppet—and shows how spectroanalysis can distinguish between the two valve types and indicate valve dysfunction as well.

Subjects and methods

Three groups of patients were studied. Group 1 comprised 15 patients with normally functioning Starr-Edwards prosthetic aortic valves with metal (titanium or 'stellite') poppets (Table 1). Group 2 comprised 3 patients with Starr-Edwards prosthetic aortic valves with metal poppets that had malfunctioned (Table 2). Group 3 comprised 13 patients with Starr-Edwards prosthetic aortic valves with non-metal (silastic) poppets with normal function (Table 3).

Echocardiographic examinations were carried out with an Ekoline 20 (Smith Kline Instruments, Inc., Palo Alto, Calif.) with a 2·25 MHz internal-focus transducer half an inch in diameter. Strip chart recordings of M-mode scan were made with a ContinuTrace multichannel recorder (Irex Medical Systems, Mahwah, N.J.) or a fibreoptic multichannel physiological recorder (Kent Cambridge Medical Limited, Ossining, N.Y.). The patients were examined while they were recumbent, with the torso raised 30°, or in the partial left lateral decubitus position. The transducer was placed in the third or fourth intercostal space along the left sternal border until the typical pattern of the anterior mitral leaflet was identified. The transducer was slowly rotated medially and superiorly until echoes from the prosthetic aortic valve were obtained. In our institution echoes from the poppet

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Table 1 *Patients with Starr-Edwards prosthetic aortic valve with metal (titanium or 'stellite') poppets with normal valve function and multiple systolic clicks*

Case No.	*Frequency (Hz) of opening and closing clicks*	*Other valvular abnormalities*
1	25 000	Mild mitral stenosis
2	2 000	Beall mitral prosthesis
3	2 000	Beall mitral prosthesis
4	2 000	None
5	16 000	None
6	16 000	None
7	16 000	None
8	4 000	None
9	16 000	None
10	2 000	None
11	8 000	Mitral stenosis with commissurotomy
12	4 000	Uncertain
13	16 000	Uncertain
14	16 000	None
15	20 000	Beall mitral prosthesis

Table 2 *Patients with Starr-Edwards prosthetic aortic valves with metal (titanium or 'stellite') poppets with valve dysfunction and absent multiple systolic clicks*

Case No.	*Other valvular abnormalities*	*Frequencies of opening and closing clicks (in Hz)*	*Comments*
1	None	16 000	68 mmHg gradient across prosthetic aortic valve at catheterisation; patient subsequently died; necropsy showed thrombus on valve
2	Beall mitral prosthesis	Opening click, 250 Closing click, 1000	Cardiac catheterisation showed poppet displaced laterally by thrombus
3	None	1000	90 mmHg gradient across prosthetic valve at cardiac catheterisation, thrombus on struts seen at surgery

Table 3 *Patients with Starr-Edwards prosthetic aortic valves with non-metal (silastic) poppets with normal valve function*

Case No.	*Frequency of opening and closing clicks (Hz)*	*Other valvular abnormalities*
1	1000	None
2	2000	None
3	2000	None
4	2000	None
5	2000	Uncertain
6	1000	Mitral commissurotomy with restenosis
7	2000	None
8	1000	None
9	1000	None
10	6000	Mild restenosis of mitral valve; tricuspid Starr-Edwards silastic valve
11	3000	Mitral and tricuspid Starr-Edwards silastic valves
12	2000	None
13	2000	Mild mitral regurgitation

were obtained in the majority of instances. It was occasionally necessary to place the transducer in the right supraclavicular fossa to obtain the clearest possible echoes from the prosthetic aortic valve. Phonocardiography was performed with a suction microphone placed at the apex of the heart.

Spectroanalysis is a method of evaluating sound emission by monitoring sound frequency and intensity (Waxler *et al.*, 1973; Gordon *et al.*, 1974). It has been used extensively in modern industry to test the function of certain machinery. The function of prosthetic valves can also be evaluated by determining the frequency profile of the opening and closing clicks for each type of prosthetic valve (Gordon *et al.*, 1974). A normally functioning prosthesis will produce opening and closing sounds at specific frequencies, depending upon the individual characteristics of that particular valve. Valve dysfunction, such as that caused by thrombus formation or tissue ingrowth (Najmi and Segal, 1965; Herr *et al.*, 1967; Hylen *et al.*, 1968, 1969, 1970; Delman, 1972), will be shown by a lower frequency than expected for that particular valve. Frequency profiles have been established in the laboratory at our institution for Starr-Edwards prosthetic valves with metal (titanium and 'stellite') and non-metal (silastic) poppets (Table 4) (Gordon *et al.*, 1974).

The spectroanalysis instrumentation is a combination of a filter system and a system for indicating the relative energy that is passed through the filter system (Gordon *et al.*, 1974). This system consists of a transducer, a preamplifier, an octave band-analyser with an output (decibel) meter, an oscilloscope, and an electrocardiograph (Gordon *et al.*, 1974). The procedure consists of using a cylindrical transducer (General Radio Company, Concord, Massachusetts) with a flat frequency response from 20 to 25 000 Hz which serves as a vibration pick-up device. The transducer was placed in the third and fourth left intercostal space 2 or 3 cm lateral to the left sternal border and was attached to an octave band noise analyser (GR type 1558 BP or GR type 1564A). An octave band is the interval between two sounds having a basic frequency ratio

Table 4 *Frequency profile of Starr-Edwards prosthetic aortic valves*

Prosthetic valve type	*Frequency of aortic opening click (Hz)*		*Frequency of aortic closing click (Hz)*	
Metal poppet ('stellite' or titanium)	> 4000	Normal	> 4000	Normal
	1000–4000	Borderline	1000–4000	Borderline
	< 1000	Abnormal	< 1000	Abnormal
Silastic poppet	> 2000	Normal	> 2000	Normal
	500–2000	Borderline	500–2000	Borderline
	< 500	Abnormal	< 500	Abnormal

of 2:1. The effective band for 1000 Hz, for example, would be from 707 to 1414 Hz. The centre band frequencies ranged from 25 to 25 000 Hz.

Results

Of the 18 patients with the Starr-Edwards prosthetic aortic valves with a metal poppet (titanium or 'stellite'), there were multiple systolic clicks in 15, as shown by phonocardiography and spectroanalysis. On auscultation, these clicks sound very much like the rapid fire from an automatic machine gun. The opening and closing sounds of each valve vary from 1000 Hz to 25 000 Hz (Tables 1, 2, and 3). The very high frequency sounds (greater than 15 000 Hz) are recorded by spectroanalysis but are not within the range of auscultation by the human ear.

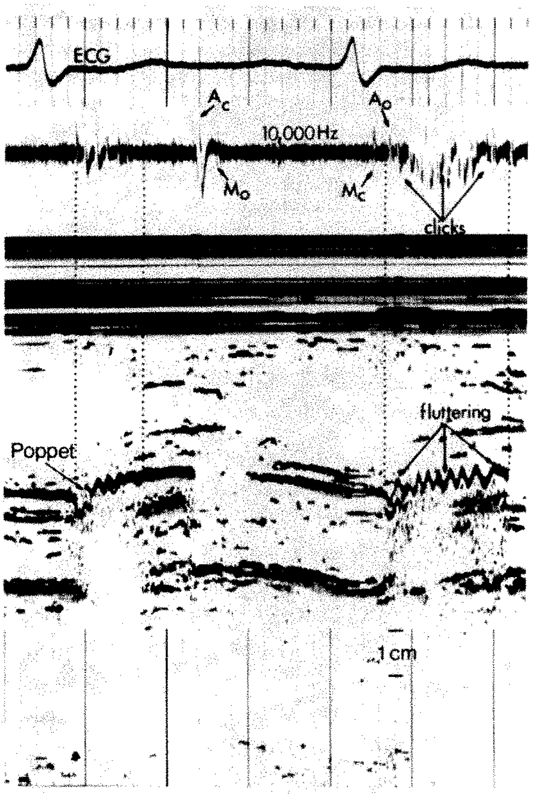

Fig. 1 *Simultaneous spectroanalysis, echocardiogram, and electrocardiogram from a patient with a Starr-Edwards prosthetic aortic valve with a metal poppet and a Beall mitral valve with a pyrolite disc. AO, aortic opening click; AC, aortic closing click; MO, mitral opening click; MC, mitral closing click. Time lines are 40 ms.*

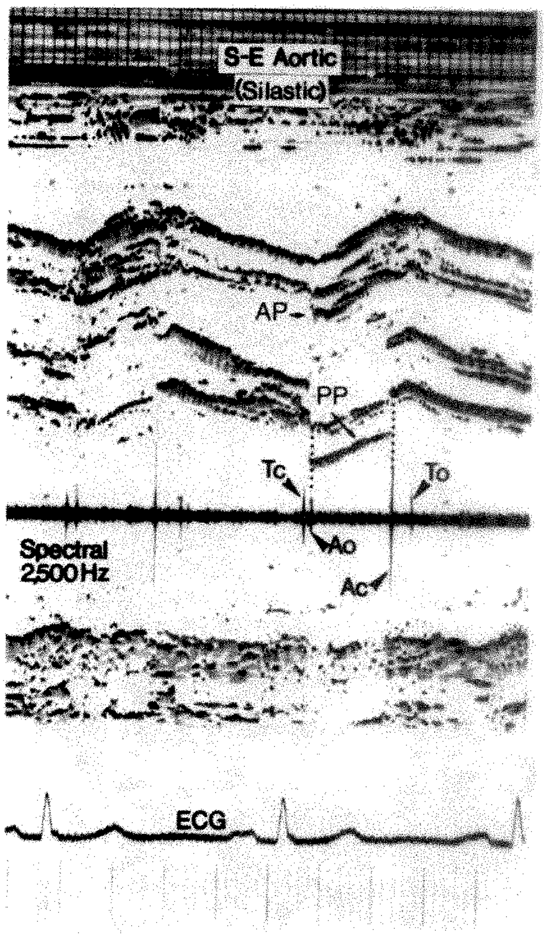

Fig. 2 *Simultaneous spectroanalysis, echocardiogram, and electrocardiogram from a patient with Starr-Edwards prosthetic aortic and tricuspid valves with silastic poppets. AO, aortic opening click; AC, aortic closing click; TO, tricuspid opening click; TC, tricuspid closing click; AP, anterior poppet; PP, posterior poppet. Time lines are 40 ms.*

An example of the multiple systolic clicks from a patient with a Starr-Edwards prosthetic aortic valve with a metal (titanium or 'stellite') poppet is seen in Fig. 1. Simultaneous spectroanalysis, echocardiogram, and electrocardiogram are represented. Numerous systolic clicks can readily be identified and are coincident with the fluttering motion of the metal poppet as shown by the echocardiogram.

Of the 18 patients with Starr-Edwards prosthetic aortic valves with metal poppets, 3 did not manifest multiple systolic clicks (Table 2). Subsequent cardiac catheterisation or surgical exploration indicated valve dysfunction. Two of the patients

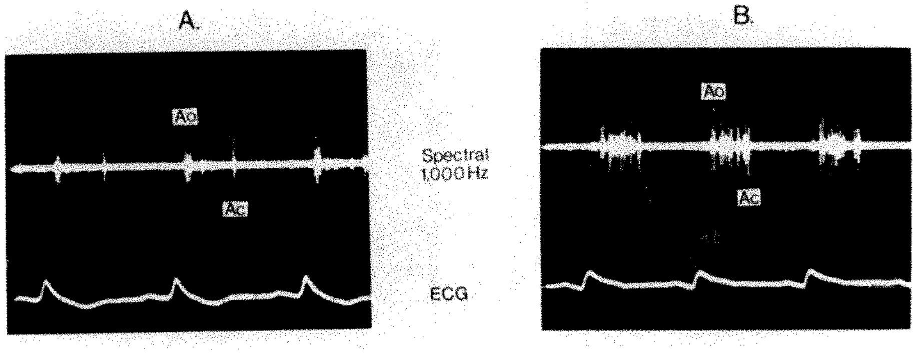

Fig 3 *Simultaneous spectroanalysis and electrocardiogram from a patient with a Starr-Edwards prosthetic aortic valve with a metal poppet which had malfunctioned (A), showing absence of multiple systolic clicks, and from a patient with normal function (B) showing multiple systolic clicks. AC, aortic closing click; AO, aortic opening click*

were found to have thrombus formation on the valve struts or ring which created a significant gradient across the valve in one of these patients (90 mmHg) and severe aortic regurgitation in the other. The third patient had a 68 mmHg gradient across the prosthetic valve, but no definite thrombus formation could be identified by aortography. This patient subsequently died, and necropsy showed thrombus formation on the prosthetic aortic valve.

All 13 patients with Starr-Edwards prosthetic aortic valves with non-metal (silastic) poppets manifested only opening and closing clicks by spectroanalysis. An example of a normally functioning valve with a non-metal poppet is seen in Fig. 2; such a valve produced only opening and closing clicks. While many of these patients manifested several systolic clicks by phonocardiography (Najmi and Segal, 1965; Dayem and Raftery, 1966a, b), these sounds were of such low frequency and intensity that they were barely recordable and hardly audible.

An example from a patient with a Starr-Edwards prosthetic aortic valve with a metal poppet which had malfunctioned is shown in Fig. 3. Multiple systolic clicks are absent, yet opening and closing clicks are clearly recorded. In 1 of the 3 patients with malfunctioning valves with metal poppets, the cut-off frequencies of the opening and closing clicks were normal (Table 2, case 1).

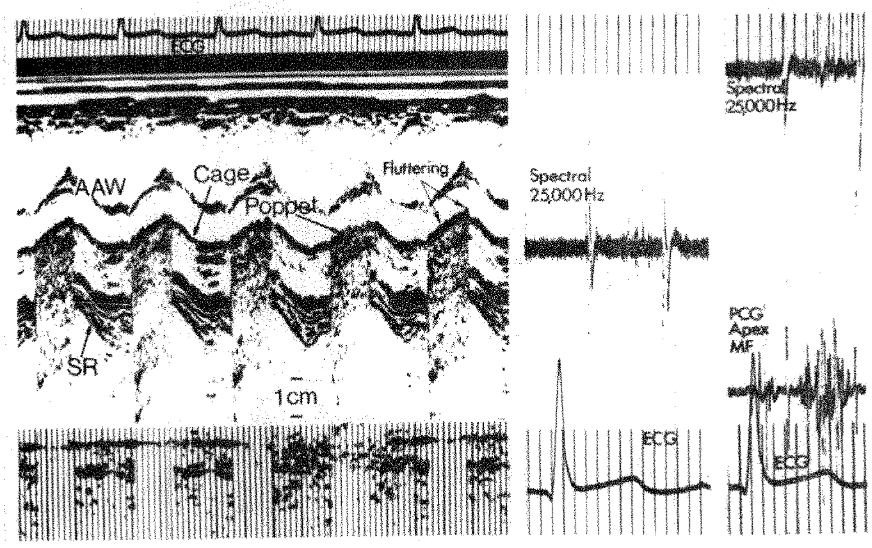

Fig. 4
Spectroanalysis, echocardiogram, phonocardiogram, and electrocardiogram from a patient with a Starr-Edwards prosthetic aortic valve with a metal poppet. Note that the systolic murmur tends to obscure the recording of multiple systolic clicks on the phonocardiogram (PCG). The clicks are well recorded by spectroanalysis. AAW, anterior aortic wall. SR, suture ring. Time lines are 40 ms.

Discussion

The technique of simultaneous echocardiography, phonocardiography, and spectroanalysis has been used to determine the function of prosthetic heart valves as well as to elucidate the mechanism of the production of sounds from these valves (Hultgren and Hubis, 1965; Najmi and Segal, 1965; Boicourt *et al.*, 1966). Cine studies of ball valve motion with a pulse simulator have shown bouncing or vibrating of the ball (Dayem and Raftery, 1966b), resulting in the production of such clicks. In patients with Starr-Edwards prosthetic aortic valves with non-metal (silastic) poppets, 2 or 3 systolic clicks of low intensity have been recorded in contrast to the high intensity multiple ejection clicks recorded from Starr-Edwards prosthetic valves with metal poppets. The 3 patients with Starr-Edwards prosthetic aortic valves with metal poppets in whom multiple systolic clicks were not heard or recorded were proved to have valve dysfunction by cardiac catheterisation or at operation.

The probable mechanism responsible for producing the multiple systolic clicks is the rapid fluttering motion of the poppet (Fig. 1). The first cardiac cycle shows the poppet fluttering only during the first half of systole corresponding with the recording of multiple systolic clicks during the same period.

During the second cardiac cycle, there is a fluttering motion of the poppet throughout systole; multiple systolic clicks are recorded coincident with the fluttering motion occupying all of systole. Reports by Dayem and Raftery (1966b) show that the poppet strikes the apex of the cage in early systole, and then collides randomly against the struts of the cage. There is some variability of this motion depending upon ejection velocity and heart rate. With rapid ejection times and fast heart rates, the ball may remain at the apex of the cage during most of the ejection period causing the systolic clicks to occur in early systole. Conversely, with a reduced ejection velocity and weaker beats, the poppet may be free to bounce and vibrate during the terminal part of systole, thereby producing additional clicks.

Systolic fluttering motion of the poppets shown by echocardiography is seen with non-metal as well as metal poppets. Exactly why metal poppets should produce easily audible multiple systolic clicks and silastic poppets do not is not entirely clear. However, this was a consistent finding in all patients with metal poppets who were examined, except the 3 in whom subsequent investigation showed prosthetic valve dysfunction.

The advantage of spectroanalysis over phonocardiography in determining the presence of multiple systolic clicks is shown in Fig. 4. While multiple systolic clicks can be recorded by phonocardiography, a systolic murmur obscures their precise identification. By setting the centre band frequency for the spectroanalysis at 25 000 Hz, the systolic murmur was effectively filtered out and the clicks are clearly identified.

The auscultatory absence of multiple systolic clicks in patients with Starr-Edwards prosthetic aortic valves with metal poppets should alert the clinician to the possibility of valve dysfunction. However, in some patients, the detection of multiple systolic clicks may be obscured by the presence of a loud systolic ejection murmur. Thus, with the combined use of echocardiography, phonocardiography, and spectroanalysis, multiple systolic clicks in relation to fluttering motion of the poppet is a normal finding in patients with Starr-Edwards prosthetic aortic valves with metal poppets. The absence of multiple systolic clicks by spectroanalysis may indicate prosthetic valve dysfunction even when the cut-off frequencies of the opening and closing clicks are normal.

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Effects of isometric exercise and increased arterial impedance on left ventricular function in severe aortic valvular stenosis[1, 2]

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Since critical aortic stenosis imposes severe obstruction to cardiac outflow, the peripheral vascular determinants of left ventricular impedance in this condition remain uncertain. Thus, the systemic arterial and left ventricular haemodynamic responses to acute circulatory interventions were evaluated during cardiac catheterisation in 10 patients with severe aortic stenosis (valve area 0·40 cm^2/m^2). Sustained isometric handgrip exercise increased systemic vascular resistance to 1278 dynes s cm^{-5} and arterial blood pressure to peak systolic 143 mmHg (mean 94), which were significantly ($P<0{\cdot}01$) greater than control (systemic vascular resistance 1110; BP peak systolic 122; BP mean 80). Isometric handgrip exercise was also accompanied by concordant changes in left ventricular pressures ($P<0{\cdot}01$) of peak systolic from 191 to 213 mmHg and end-diastolic from 16 to 23 mmHg; cardiac output (5·62 l/min) and peak systolic left ventricular aortic gradient (69 mmHg) were unchanged ($P>0{\cdot}05$). In 7 of these patients intravenous phenylephrine infusion (2·7 to 6·0 μg/min) produced the following responses similar ($P>0{\cdot}05$) to isometric handgrip exercise: increases ($P<0{\cdot}01$) in systemic vascular resistance to 1549, BP to peak systolic 150 and mean 97, and left ventricular pressures to peak systolic 211 and end-diastolic 22 ($P<0{\cdot}02$) without alterations in cardiac output or peak systolic LV-aortic gradient; isometric handgrip exercise was accompanied by an increase ($P<0{\cdot}01$) in contractile state indices (peak dp/dt 1882 to 2580 mmHg/s; Vmax 4·28 to 6·43 circ/s) and rise in heart rate (72 to 82 bpm) while these variables remained constant ($P>0{\cdot}05$) with phenylephrine. Therefore, augmentation of arterial resistance increased left ventricular impedance resulting in abnormalities of cardiac haemodynamics despite the presence of pronounced valvular obstruction. These observations are of potential importance in the pathogenesis of sudden death in severe aortic stenosis and provide therapeutic insight in emergency medical management of ventricular dysfunction in this condition.

Recent investigations have emphasised the importance of vascular impedance in the regulation of left ventricular function (Mason, 1973; Miller *et al.*, 1975; Williams *et al.*, 1975). Thus decrease in systemic arterial resistance with a variety of peripheral vasodilator agents has been shown to enhance pump performance in patients with cardiac dysfunction with coronary heart disease, valvular and ischaemic mitral regurgitation, and aortic valvular regurgitation (Majid *et al.*, 1971; Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973; Chatterjee and Swan, 1974; Cohn *et al.*, 1974; Miller *et al.*, 1975, 1976a, b). In these clinical settings afterload reduction results in improved left ventricular performance by increasing depressed ejection fraction and raising effective stroke output concomitant with lessened myocardial oxygen requirements. However, since severe valvular aortic stenosis poses a fixed obstruction to left ventricular ejection which might obviate the cardiac response to peripheral circulatory changes, the relation between ventricular function and systemic vascular dynamics in this condition is unknown. Therefore, to evaluate the control and determinants of left ventricular performance in aortic stenosis, the present study was undertaken to assess the haemodynamic response to acute rises

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in arterial impedance in this form of systolic pressure overload.

Subjects and methods

PATIENTS

The data for this study were obtained from 10 consecutive patients with isolated critical valvular aortic stenosis undergoing diagnostic cardiac catheterisation and coronary arteriography. All patients were without angiographic evidence of other valvular dysfunction, coronary arterial obstruction, or segmental ventricular dyssynergy. There were 8 men and 2 women whose ages ranged from 43 to 72 years (mean 58 years). Clinical symptoms included cerebral ischaemia, 6 patients; cardiac decompensation, 3 patients; and angina pectoris, 7 patients. Functional classification by the criteria of the New York Heart Association was Class I, 5 patients; Class II, 3 patients; and Class III, 2 patients. All patients voluntarily gave informed consent for the present study.

CARDIAC CATHETERISATION

Each of the patients underwent diagnostic right and retrograde left heart catheterisation without systemic premedication. All left ventricular pressure recordings were obtained using the high-fidelity micromanometer-tip catheter (Millar Instruments, Inc., Houston, Texas) possessing a frequency response of 20 kHz. The first derivative of left ventricular pressure (dp/dt) was obtained by an electronic differentiator with a linear amplitude response above 500 Hz. Lead II of the external electrocardiogram was recorded. Cardiac output was measured in duplicate by the indicator dilution technique using indocyanine green dye injected into the left ventricle with brachial arterial sampling. The brachial artery phasic and mean pressures, obtained by the No. 18 Longdwell needle, were shown to be the same as the central aortic pressures in each patient. Systemic arterial pressure was recorded using the Statham P23Db transducer which enabled frequent measurements of the transaortic valvular gradient. The aortic valve area, calculated by the Gorlin formula (Gorlin and Gorlin, 1951), was the same in each individual using either the simultaneous left ventricular-brachial artery or left ventricular-ascending aortic pressure gradients.

ISOMETRIC HAND GRIP

All patients were familiarised with the handgrip dynamometer (Asimow Engineering Co., Los Angeles, California) and its utilisation before catheterisation. After the recording of control haemodynamic data, the patients exerted maximum instantaneous force on the dynamometer which was followed by sustained grasp at 30 per cent of their peak handgrip exertion for a total period of 5 minutes. Normal ventilation was maintained during the isometric exercise period with avoidance of the Valsalva manoeuvre. All cardiocirculatory measurements were repeated during the final minute of sustained static exercise.

PHENYLEPHRINE INFUSION

After the cessation of isometric exercise, haemodynamics promptly returned to the control state, which were allowed to be maintained for at least an additional 10 minutes. Subsequently in 7 of the 10 patients phenylephrine was administered intravenously (range 2·7 to 6·0 μg/min; mean 3·0 μg/min) to reproduce the same rise in systemic arterial pressure as occurred during isometric handgrip exercise. Patients were stabilised at this increased level of systemic arterial pressure by constant phenylephrine infusion for 5 minutes, during the final minute of which cardiac and systemic haemodynamics were again assessed.

HAEMODYNAMIC MEASUREMENTS

The following values were measured or calculated during the periods of control, isometric exercise, and phenylephrine infusion: cardiac index; stroke index; left ventricular stroke work index (Snell and Luchsinger, 1965); systemic vascular resistance (Miller *et al.*, 1975); and tension-time index (Sarnoff *et al.*, 1958). Further, left ventricular force-velocity relations were calculated from 5 consecutive contractions using the high-fidelity recordings of ventricular pressure and simultaneous dp/dt at 5 ms intervals during isovolumic systole (Mason *et al.*, 1971). Contractile element velocity (Vce) was determined by the Maxwell three component muscle model and the Vmax contractility index was estimated by extrapolation of the Vce-developed pressure curve to zero load by means of a polynomial regression equation (Mason *et al.*, 1970). In addition, left ventricular peak dp/dt (Mason, 1969) was obtained. All data and the interventions were carried out before contrast angiography. Student's t test for paired data was used for analysis of statistical significance.

Results

CONTROL HAEMODYNAMICS

Control haemodynamic data are presented in the Table. All patients had critical aortic stenosis as indicated by pronounced transvalvular gradients (average peak systolic 69 mmHg; range 44 to 123) with severe reduction of aortic valve area index (average:

Table *Cardiocirculatory changes during isometric exercise and phenylephrine infusion*

Patients		*HR*	*SBP*	*DBP*	*MBP*	*SV*	*SI*	*CO*	*CI*	*LVEDP*	*LVSP*	*LVSWI*	*SVR*	*GRAD*	*Vmax*	*dp/dt*
JK	—Control	70	113	52	75	69	37	4·4	2·6	16	157	77	1291	44	3·68	1900
	ISH	78	132	70	91	69	38	5·4	3·0	27	180	78	1288	48	8·06	3400
	PH	65	119	63	80	66	36	4·3	2·3	17	165	68	1413	46	3·73	1600
CG	—Control	84	105	55	71	66	36	5·6	2·8	15	158	71	961	53	3·51	1500
	ISH	84	123	62	83	63	32	5·4	2·7	31	173	74	1181	50	7·78	2000
	PH	60	140	68	85	61	31	3·7	1·8	31	190	75	1751	50	3·77	2000
JR	—Control	90	156	55	88	54	31	4·8	2·8	11	217	92	1411	61	3·88	1475
	ISH	100	164	65	99	47	27	4·7	2·7	14	228	79	1627	64	9·47	2300
	PH	90	170	70	102	45	26	4·5	2·6	13	225	75	1756	55	4·01	2800
SG	—Control	73	130	50	75	62	32	4·5	2·4	18	214	85	1280	84	3·77	1600
	ISH	100	157	63	93	64	33	6·2	3·4	36	245	94	1167	88	5·84	1800
	PH	70	166	79	110	76	40	5·3	2·8	28	250	114	1554	84	4·27	1100
VM	—Control	60	115	70	85	93	52	5·6	3·1	23	195	122	1171	80	4·48	2000
	ISH	70	142	80	100	80	45	5·6	3·2	30	222	117	1385	80	4·84	2300
	PH	54	125	76	90	85	48	5·6	2·6	22	205	120	1513	80	4·45	2160
MA	—Control	70	170	72	107	101	53	7·1	3·7	17	230	153	1171	60	3·61	2660
	ISH	76	189	79	112	76	40	5·8	3·0	17	246	124	1503	57	5·99	3660
	PH	70	200	85	117	84	44	5·9	3·1	26	260	140	1545	60	4·62	2330
AE	—Control	60	108	60	76	83	41	5·4	2·7	15	160	81	1168	52	4·20	2160
	ISH	72	136	80	92	76	37	5·5	2·7	20	190	87	1294	54	5·80	2740
	PH	60	130	75	95	93	46	5·6	2·7	20	183	102	1314	53	4·43	2290
LP	—Control	70	110	62	78	85	46	6·4	3·4	14	173	99	913	63	6·98	2100
	ISH	78	132	73	90	74	40	5·9	3·2	16	194	95	1149	62	7·00	2300
VD	—Control	60	105	55	74	80	39	5·2	2·6	13	171	84	969	66	4·64	1600
	ISH	70	136	71	93	69	33	4·8	2·3	17	204	86	1404	68	5·88	2800
GS	—Control	84	108	56	75	86	47	7·2	4·2	20	231	134	766	123	4·10	1830
	ISH	90	120	70	85	89	48	8·0	4·4	18	243	148	790	123	3·60	2000
Average ±SEM																
	Control	72	122	59	80	78	41	5·62	3·03	16	191	100	1110	69	4·28	1882
		±3	±7	±3	±3	±5	±3	±0·29	±0·18	±1	±10	±9	±63	±7	±0·32	±116
	ISH	82	143	71	94	71	37	5·73	3·06	23	213	98	1278	69	6·43	2580
		±4*	±7*	±2*	±3*	±4†	±2*	±0·30	±0·18	±2*	±9*	±8	±73*	±7	±0·54*	±194*
	PH	67	150	74	97	73	39	4·99	2·56	22	211	99	1549	61	4·18	2040
		±4	±10*	±3*	±5*	±6	±3	±0·32	±0·16	±2†	±13*	±10	±61*	±6	±0·13	±204

Abbreviations: ISH, isometric handgrip exercise; PH, phenylephrine; HR, heart rate, beats/min; SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); MBP, mean blood pressure (mmHg); SV, stroke volume (ml); SI, stroke index, ml/m^2; CO, cardiac output, l/min; CI, cardiac index, l/min per m^2; LVEDP, left ventricular end-diastolic pressure (mmHg); LVSP, left ventricular peak systolic pressure (mmHg); LVSWI, left ventricular stroke work index, g·m per m^2; SVR, systemic vascular resistance, dynes s cm^{-5}; GRAD, peak systolic left ventricular-aortic gradient (mmHg); Vmax, circumferences/s; dp/dt, maximum rate of isovolumic left ventricular pressure rise (mmHg/s); *$P < 0·01$; †, $P < 0·02$.

0·40 cm^2 per m^2; range: 0·25 to 0·49). There were mild to moderate rises in left ventricular end-diastolic pressure in 9 of the 10 individuals (average 16 mmHg). Cardiac index was normal in all but one patient in whom it was minimally decreased (average 3·03 l/min per m^2). Left ventricular ejection fraction was greater than 60 per cent in 6 patients and above 40 per cent in the remaining 4 subjects (average 62 per cent).

ISOMETRIC HANDGRIP

The cardiocirculatory responses induced by sustained isometric exertion are shown in the Table. Handgrip exercise resulted in significant rises ($P < 0·01$) in systolic, diastolic, and mean systemic arterial pressures. Since cardiac index remained unaltered ($P > 0·05$), total systemic vascular resistance rose substantially from 1110 to 1278 dynes sec cm^{-5} ($P < 0·01$). There were concordant increases in the systemic arterial and left ventricular systolic pressures; thereby the peak systolic gradient across the aortic valve remained constant ($P > 0·05$) (Fig. 1A). Further, as indicated in Fig. 1B, in each patient there was a close correlation between the rises in both the left ventricular and systemic arterial systolic pressures during isometric exertion ($r = 0·94$). Static handgrip resulted in a slight rise in heart rate ($P < 0·05$) (Fig. 2A); stroke index declined ($P < 0·01$) (Fig. 2B); while ventricular stroke work remained unchanged ($P < 0·05$). These haemodynamic changes were accompanied by a significant rise in left ventricular end-diastolic pressure ($P < 0·01$) (Fig. 2C) and a pronounced rise in the tension-time index ($P < 0·01$) (Fig. 2D).

PHENYLEPHRINE INFUSION

All haemodynamic data recorded after termination of isometric exercise and immediately preceding phenylephrine infusion were the same as those in the initial control period for each patient (Table). Phenylephrine administration provoked substantial peripheral vasoconstriction as indicated by the augmentations in systemic blood pressure ($P < 0·01$) and systemic vascular resistance ($P < 0·01$). Thereby

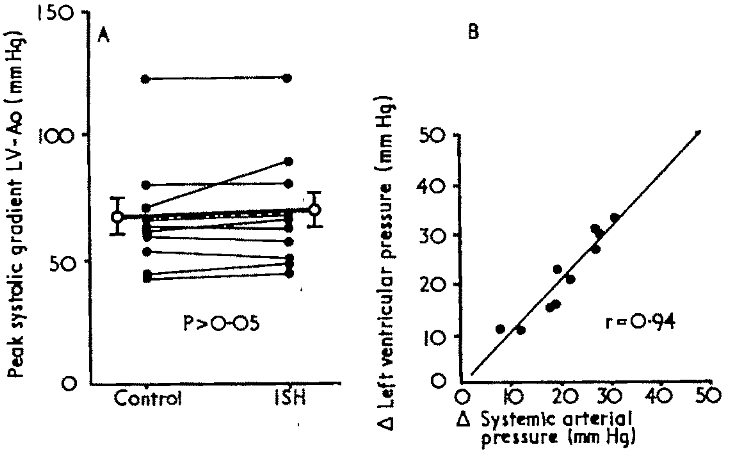

Fig. 1 *Left ventricular (LV) response to isometric exertion (ISH) in severe aortic stenosis. Panel A indicates that no change occurred in peak systolic left ventricular-aortic (Ao) pressure gradient during ISH. Panel B shows the relation between increase in arterial and increase in LV peak systolic pressure during ISH. Thus, increased systemic arterial resistance and blood pressure imposed additional aortic impedance and afterload burden on the left ventricle despite the presence of critical aortic stenosis.*

this alpha-adrenergic agonist resulted in alterations of peripheral circulatory dynamics which were similar (P >0·05) to the systemic arterial response provoked by isometric exertion. Complete data on the cardiac response to phenylephrine infusion are provided in the Table. Though the changes in left ventricular pressures (peak systolic, end-diastolic, and transaortic peak systolic gradient) did not differ between phenylephrine and handgrip stress, the response to the drug infusion was not associated with alteration (P >0·05) in either heart rate or left ventricular contractility indices.

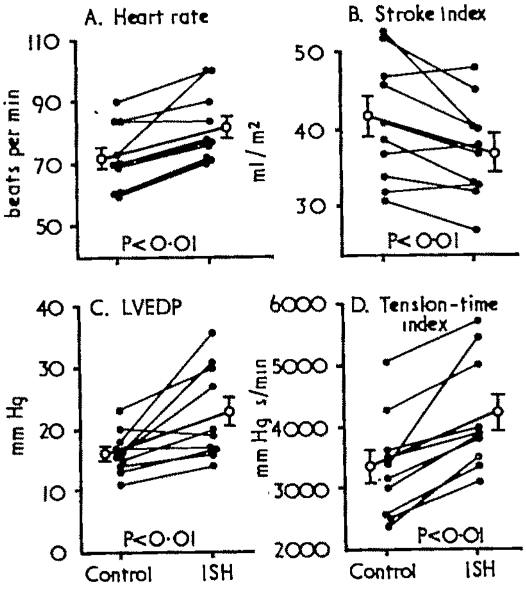

Fig. 2 *Left ventricular response to ISH in aortic stenosis. Panel A shows that static exertion provoked a significant rise in heart rate. Since cardiac output remained unchanged, stroke index decreased (Panel B). The haemodynamic burden imposed by ISH on left ventricular function is shown in the lower panels; left ventricular end-diastolic pressure (LVEDP) (Panel C) and tension-time index (Panel D) increased in all patients.*

Discussion

The present investigation emphasises the integral relation between peripheral circulatory dynamics and cardiac pump performance even in the presence of aortic stenosis. Specifically our findings document that an acute rise in systemic vascular resistance accompanied by a rise in arterial blood pressure imposes a substantial burden on left ventricular function despite the presence of critical obstruction to aortic outflow. Therefore, an important observation shown in the Table and Fig. 1 is that in aortic stenosis left ventricular impedance is determined by systemic arterial resistance as well as the fixed valvular obstruction.

This investigation also provides an understanding of the cardiocirculatory changes which occur with static exercise in critical aortic stenosis. Though other studies have measured the cardiac response to isometric exertion in a number of clinical conditions (Lind and McNicol, 1968; Lind, 1970; Helfant *et al.,* 1971; Krayenbuehl *et al.,* 1972; Stefadouros *et al.,* 1974), the effects of this intervention in patients with aortic stenosis have not been assessed previously. Since the haemodynamic consequences of isometric exercise are influenced by the extent and duration of sustained contraction, rather than the site or total mass of the active skeletal muscle (Donald *et al.,* 1967), the isometric procedure used in this study provided a potent form of static stress (Lind and McNicol, 1967). In normal subjects sustained contraction greater than 15 per cent of the voluntary maximum has been shown to produce a consistent cardiac response which includes a pronounced rise in systemic arterial blood pressure, increased heart rate, and raised cardiac output while the systemic vascular resistance remains unchanged (Donald *et al.*, 1967). Though the exact mechanisms of these cardiovascular changes have not been clarified, studies by Lind and associates have implicated a centrally mediated neurocirculatory mechanism by which the high systemic arterial pressure provides perfusion of the active skeletal muscle despite mechanical compression of the vascular bed in the involved musculature (Donald *et al.*, 1967; Lind and McNicol, 1967). Thus, the normal left ventricle responds to isometric stress with an increase in stroke work index using enhanced inotropic activity while cardiac preload remains constant (Stefadouros *et al.*, 1974).

In contrast, our present investigation shows that isometric exertion produces a deleterious effect on left ventricular performance in patients with severe aortic stenosis. Therefore, as indicated by the rise in cardiac tension-time index and the other variables related to myocardial energetics (Fig. 2), left ventricular oxygen requirements were shown to be considerably greater during handgrip exertion than in the control period. The major factors responsible for this rise in cardiac oxygen demands include the augmentation in systemic vascular resistance and arterial blood pressure combined with a faster heart rate. Furthermore, the increase in cardiac preload and the concomitant enhancement of the indices of left ventricular contractility also principally contributed to the greater myocardial oxygen needs. Nevertheless, since cardiac stroke index declined and ventricular stroke work failed to rise appropriately, static exertion resulted in impaired ventricular performance and efficiency.

These haemodynamic changes are consistent with previous studies of static exertion in patients with ventricular dysfunction unrelated to aortic stenosis (Amende *et al.*, 1972). For example, the study of patients with ventricular volume overload or coronary artery disease by Amende and colleagues showed that sustained handgrip was accompanied by a significant rise in left ventricular end-diastolic pressure without a change in stroke work index (Amende *et al.*, 1972). Similarly, this same response was also observed in patients with heart disease by Kivowitz *et al.* (1971). In addition, these investigators were able to correlate the isometric-induced haemodynamic abnormalities with the severity of clinical functional impairment, and thereby concluded that isometric handgrip provided a simple haemodynamic assessment of left ventricular contractile reserve.

Since isometric exertion provokes a number of simultaneous cardiovascular responses (Donald *et al.*, 1967; Lind and McNicol, 1967; Amende *et al.*, 1972; Stefadouros *et al.*, 1974), it was the intent of the present study to evaluate further the left ventricular response to acute isolated changes in peripheral resistance in aortic stenosis. The dose regimen of phenylephrine administered provided peripheral alpha-adrenergic receptor stimulation without direct pharmacological cardiac action (Eckstein and Abboud, 1962; Kivowitz *et al.*, 1971). Infusion of this agent in 7 of our patients resulted in a rise in systemic arterial pressure and vascular resistance to levels that were similar to those provoked by isometric exertion (Table). Haemodynamic measurements during constant phenylephrine administration indicated that the left ventricular systolic pressure and transaortic gradient responses were similar to those produced by hand grip exercise. Thus, this pharmacological intervention provides confirmatory evidence that ventricular function in critical aortic stenosis is directly influenced by changes in systemic vascular impedance.

It is important to emphasise the potential clinical implications of the haemodynamic responses observed herein. Since isometric exertion caused acute depression in ventricular performance in our aortic stenosis patients, these data provide a potential pathophysiological explanation for sudden death which is a recognised clinical hallmark in this condition and has been described during static exertion (Schwartz *et al.*, 1969). Thus, the combination of increased myocardial oxygen requirements and reduced stroke index during isometric exertion may result in further imbalance of the already jeopardised myocardial oxygen supply-to-demand relation, with resultant fatal ventricular arrhythmias. Further, rapidly occurring death in this clinical condition has also been attributed to a progressive low output state which precedes terminal arrhythmias (Schwartz *et al.*, 1969). Since even the isometric exertion of short duration conducted in this study induced pronounced haemodynamic impairment, it is possible that even more severe static exertion might result in a deleterious cycle of rising systemic impedance with consequent failing cardiac output. Furthermore, the data also provide important therapeutic insights for additional evaluation. Since the present study establishes the interrelation between left ventricular and peripheral vascular dynamics in critical aortic stenosis, reduction in systemic impedance by pharmacological means may provide a temporary but potentially life-saving medical adjunct for improving depressed cardiac performance which could afford additional time for definitive surgical therapy in this condition.

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Dual effect of disopyramide on atrial and atrioventricular conduction and refractory periods

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Disopyramide has been shown in conditions of cholinergic blockade to have a depressant effect upon sinus node automaticity and the atrial refractoriness. It also prolongs atrioventricular conduction and increases atrioventricular refractoriness. These effects may often be masked in vivo *by the anticholinergic effects of the drug.*

Disopyramide[1] is an antiarrhythmic compound which is effective against both ventricular and supraventricular arrhythmias (Jennings *et al.*, 1976; Mizgala and Huvell, 1976) and may also be of value in tachyarrhythmias related to the Wolff-Parkinson-White syndrome (Spurrell *et al.*, 1975).

It has been shown *in vitro* to reduce the maximum rate of depolarisation in both atrial (Sekiya and Vaughan Williams, 1963) and ventricular tissues (Yeh *et al.*, 1973) and is a local anaesthetic. It is thus an antiarrhythmic drug of the first class. In addition, it slightly prolongs the duration of the atrial action potential *in vitro* (Sekiya and Vaughan Williams, 1963) and *in vivo* (Edwards *et al.*, 1976) (Class 3 action). A drug possessing membrane stabilising properties on atrial and ventricular tissue might be expected to prolong the functional refractory period. Though such an effect has been shown in the ventricles in man (Spurrell *et al.*, 1975), there has been considerable disagreement concerning the action of this compound upon sinus node, atrial, and atrioventricular nodal function. It has been suggested that the variability of the electrophysiological responses of these tissues to the drug may be the result of an atropine-like action of disopyramide (Sekiya and Vaughan Williams, 1963) which would shorten atrial and atrioventricular nodal conduction time, especially if vagal tone was high, and thus mask the direct depressant effect of the compound.

The present study was undertaken to investigate the effect of intravenously administered disopyramide when the parasympathetic control of the heart had already been antagonised by atropine, in order to allow any direct depressant effect of the compound to become manifest. Thus the relative contribution of the two actions could be assessed.

Patients and methods

Fourteen patients were studied (Table 1). Twelve had clinical or electrocardiological evidence of arrhythmias and the primary investigation was the study of the arrhythmias. One had mild pulmonary stenosis, and underwent right heart catheterisation, and another patient had ischaemic heart disease. All gave informed and written consent to the further procedures described here. None was receiving any cardioactive or other medication, and all were studied in a fasting state.

A quadripolar pacing catheter (USCI 5F) was introduced percutaneously into the right femoral vein and advanced to the high right atrium under fluoroscopic control. The distal pair of electrodes was used to pace the high right atrium at the junction with the superior vena cava. The proximal pair of electrodes recorded a high right atrial electrogram. A second, bipolar, pacing electrode (USCI 5F/6F) was introduced percutaneously via the right femoral vein and advanced under fluoroscopic control through the tricuspid valve to a position suitable for recording the His bundle deflection. The intracardiac potentials were recorded, suitably filtered, together with three surface electrocardiographic leads (Standard leads I, II, III, or V1), using an Elema-Schonander Mingograph 82 at a paper speed of 100 mm s^{-1}. Pacing and programmed stimuli, of 2 ms duration and twice threshold strength, were delivered by a specially-built stimulator, based on the Grass S44 module.

The high right atrium was paced at rates of 110, 130, 150 min^{-1} (1·8, 2·2, and 2·5 Hz). Sinus node recovery time was measured as the time from the

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[1] Rythmodan, Roussel.

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Table 1

Case No.	*Sex*	*Age (y)*	*Diagnosis*
1	M	51	Sick sinus syndrome
2	M	16	Mild pulmonary stenosis
3	M	50	Coronary artery disease
4	M	50	Paroxysmal atrial tachycardia
5	M	42	Paroxysmal atrial fibrillation, mild mitral stenosis
6	F	60	Sick sinus syndrome
7	F	59	Sick sinus syndrome
8	M	45	Re-entrant atrioventricular nodal tachycardias
9	M	54	Adams-Stokes attacks, right bundle-branch block with normal axis
10	M	20	Normal heart
11	F	42	Paroxysmal atrial tachycardias
12	M	55	Recurrent ventricular fibrillation, coronary artery disease
13	F	18	Lown-Ganong-Levine syndrome
14	F	76	Right bundle-branch block and left axis deviation

last stimulus of a 2 min train at 150 min^{-1} (2·5 Hz) to the onset of the first spontaneous sinus impulse. The refractory periods of the atrium and atrioventricular node were determined during fixed rate pacing by the introduction of premature stimuli (St 2). The fixed driving rate employed was in the range 1·6 to 2·1 Hz (600 to 475 ms RR intervals), and was constant for each patient. Heart rate, sinus node recovery time, atrial and atrioventricular conduction times, and the refractory periods of the atrium and atrioventricular node were measured under basal conditions, and after the intravenous injection of atropine sulphate, 0·025 mg kg^{-1}. Measurements were then repeated after the intravenous injection (over 2 min) of disopyramide 2 mg kg^{-1}.

Measurements were completed within 15 minutes of the end of the injection, at which time plasma concentration would be expected to be within the therapeutic range (Ward and Kinghorn, 1976; Spurrell *et al.*, 1975).

Definitions

R–R: the cycle length of the paced or spontaneous rhythm, in ms.

HRA–LRA: the time in ms from the origin of the high right atrial potential to the origin of the low right atrial potential seen on the His bundle electrogram, representing right atrial conduction time.

LRA–H: the time in ms from the low right atrial potential seen on the His bundle electrogram to the His potential, representing atrioventricular-nodal conduction time.

St1–St2: the time in ms between a pacing stimulus and a premature stimulus.

ERP atrium: the effective refractory period of the atrium is the longest St1–St2 interval that does not result in atrial depolarisation by St2.

ERP–AVN: the effective refractory period of the atrioventricular node is the longest LRA1–LRA2 interval that does not result in conduction of LRA2 to the bundle of His.

FRP–AVN: the functional refractory period of the atrioventricular node is the shortest H1–H2 interval resulting from two atrial depolarisations.

Results

These are summarised in Tables 2 and 3.

The mean sinus node recovery time was shortened by atropine from 947±321 to 714±167 ms ($P<0·01$; n=7), and the mean heart rate increased from 70±18 to 105±27 beats per min ($P<0·001$; n=14). The mean ERP of the atrium was shortened from 258±31 to 232±33 (NS; n=9). The FRP of the atrioventricular node was shortened from 429±68 to 355±38 ms ($P<0·01$; n=9).

All the results reported in the following section refer to the effect of disopyramide 2 mg kg^{-1} in patients who had been pretreated with atropine 0·025 mg kg^{-1}.

The mean sinus node recovery time was prolonged from 714±167 to 826±223 ms ($P<0·01$; n=7). The mean heart rate was reduced from 105±27 to 87±23 per min ($P<0·001$; n=14). The mean ERP of the atrium was increased from 232±33 to 268±43 ms ($P<0·01$; n=9). The LRA–H interval in sinus rhythm was prolonged from 80±15 to 91±16 ms ($P<0·01$; n=14). With high right atrial pacing at 130 min^{-1} (2·2 Hz) the prolongation was more pronounced, being from 78±33 to 148±76 ms ($P<0·05$; n=7). The ERP of the atrioventricular node could only be measured on 2 out of 9 occasions in 7 patients when this was longer than the ERP of the atrium. The FRP of the atrioventricular node was much increased from 355±38 to 423±54 ms ($P<0·001$; n=9). There were small and insignificant changes in intra-atrial and His-Purkinje conduction times.

Table 2 *Values for heart rate, sinus node recovery time, and intracardiac conduction time*

	Basal	*Atropine (0·025 mg/kg)*	*Disopyramide (2 mg/kg)*	
Heart rate	70 ±18 min	105 ± 27	87 ± 23	n=14
Sinus node recovery time	947 ± 32 ms	714 ±167	826 ±223	n=7
HRA–LRA	39 ±12 ms	36 ± 8	39 ± 9	n=8
LRA–H	92 ±20 ms	80 ± 15	91 ± 16	n=14
	123 ±34 ms*	87 ± 23*	120 ± 43*	n=7
	137 ±36† ms	78 ± 33†	148 ± 78†	n=7
HV	49 ± 7 ms	47 ± 9	50 ± 8	n=14

*During high right atrial pacing at 110 min^{-1}.
†During high right atrial pacing at 130 min^{-1}.

Table 3 *Effective refractory period of atrium and functional refractory period of atrioventricular node measured in milliseconds*

Case No.	*Driving rate*	*ERP of atrium (ms)*			*FRP of AVN (ms)*		
		Basal	*Atropine*	*Disopyramide*	*Basal*	*Atropine*	*Disopyramide*
1	600	330	205	220	550	400	450
2	475	275	165	210	375	335	350
3	475	230	250	210	375	290	330
4	500	275	225	300	470	415	470
5	500	230	255	290	415	370	415
6	500	250	285	325	510	345	445
7	600	240	225	270	435	375	500
8*	550	255	240	290	385	340	440
	500	240	240	300	350	330	410
	430	230	240	255	415	370	455
Mean and SEM		258 ±31	232 ±33 NS	268 ±43 P<0·01	429 ±68	355 ±38 P<0·01	423 ±54 P<0·001

*Case 8 was studied at three driving rates

Discussion

Intracellular studies on isolated rabbit atria (Sekiya and Vaughan Williams, 1963) and isolated ventricular fibres (Yeh *et al.*, 1973) of the effect of disopyramide have shown 'membrane stabilising' properties indicating that the drug is an antiarrhythmic agent of the first class (Vaughan Williams, 1975). It is also a local anaesthetic. Sekiya and Vaughan Williams (1963) also showed a prolongation of action potential duration (class 3 action), during intracellular recording on rabbit atria, which has been confirmed in the anaesthetised dog by Edwards *et al.* (1976) recording monophasic action potentials with suction electrodes. The expected findings in man with a compound having the above properties would be a prolongation of atrial, atrioventricular nodal, and ventricular refractoriness. While Spurrell *et al.* (1975) have shown a clear-cut prolongation in the refractory period of the ventricle, there has been considerable variation in the reported effects of disopyramide upon sinus node automaticity, atrial and atrioventricular conduction times, and refractory periods.

Befeler *et al.* (1975) have shown a modest reduction in sinus node recovery time 15 minutes after administration, but which later increased to 146 ms 30 minutes after administration. If this reduction in sinus node recovery time had been the result of the anticholinergic properties of disopyramide then it might have been expected that the sinus rate would also have increased, but the authors state that the basic sinus rate was not altered. In the present study a fall in heart rate has been noted together with a prolongation of the sinus node recovery time, results which are both in accord with *in vitro* studies.

Spurrell *et al.* (1975) found that the disopyramide produced pronounced prolongation in the effective refractory period of the atrium in 7 patients. On the other hand, Josephson *et al.* (1973) did not see consistent changes; in 24 measurements in 12 patients the atrial effective refractory period was prolonged in 13, shortened in 6, and unchanged in 5. There was a small mean prolongation of 13 ms. Similarly, Befeler *et al.* (1975) did not observe consistent changes, but noted a small mean shortening of the atrial effective refractory period of 30 ms. The present study showed a mean prolongation of atrial effective refractory period from 232 ±33 to 268 ± 43 ms.

All these apparently conflicting results may be reconciled. After cholinergic blockade with atropine the prolongation of atrial effective refractory period shown in this study is in agreement with the depressant action on conduction reported in studies *in vitro*. It is apparent that *in vivo* the total effect of disopyramide depends upon the degree of vagal tone. If this is high then the anticholinergic action of disopyramide predominates, and the resultant effect is a shortening of the atrial effective refractory period. When vagal action is abolished by atropine then the direct depressant action of disopyramide is shown and a lengthening of atrial effective refractory period is observed.

Variable effects of disopyramide have also been reported on atrioventricular conduction and refractory periods. Josephson *et al.* (1973) found disopyramide shortened the effective refractory period of the atrioventricular node and was without effect on the functional refractory period. Marrott *et al.* (1975) did not find any consistent alteration in the effective refractory period of the atrioventricular node. Befeler *et al.* (1975) also found the effective refractory period of the atrioventricular node to be unchanged after disopyramide but showed a small increase in the functional refractory period of the atrioventricular node. In the present work, after cholinergic blockade, disopyramide produced a consistent and pronounced prolongation in the functional refractory period of the atrioventricular node of 68 ±34 ms. There was also a prolongation of the resting LRA–H interval of 11 ±5 ms, and this prolongation became even more pronounced during high right atrial pacing.

These results suggest that, after cholinergic blockade, disopyramide exerts purely depressant effects upon the sinus node, atrium, and atrioventricular node. It is suggested that the variable results previously shown can be explained by the interaction of the blockade of intrinsic vagal tone and the direct depressant effect of disopyramide.

The question arises, if this interpretation is accepted, whether it could provide a rational basis for the selection of the types of arrhythmia where disopyramide might be appropriate. From the present study it appears that disopyramide should be effective in areas where there is no parasympathetic innervation, such as the His-Purkinje system, ventricular myocardium, and the accessory pathways found in pre-excitation syndromes. This conclusion is in agreement with the empirical clinical findings of several workers.

The anticholinergic effect may also be of value in arrhythmia prophylaxis after myocardial infarction when atrioventricular conduction delay may be a problem (Jennings *et al.*, 1976).

A proviso should be made on the above conclusions. This study observed the effects of disopyramide during the first 15 minutes after administration. No published human work has assessed the effect of disopyramide upon the conduction system for longer than 30 minutes. Edwards *et al.* (1976) have shown in anaesthetised dogs that monophasic action potentials (a measure of the intracellular action potential) recorded with suction electrodes did not achieve maximum prolongation after disopyramide until 30 to 45 minutes after administration. This suggests that previous human studies may have mainly related to the effects of class 1 actions of diosopyramide and that the class 3 actions, if of slower onset, may have been underestimated. Amiodarone, a compound having predominantly class 3 actions, has significant antiarrhythmic actions against atrial arrhythmias (Olsson *et al.*, 1973), and thus the class 3 actions possessed by disopyramide may be of similar importance.

Although the present study may explain the inconsistencies noted between previous reports on the basis of the dual action of disopyramide the full electrophysiological effect of disopyramide including the class 3 actions has not yet been fully elucidated.

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Left ventricular filling in hypertrophic cardiomyopathy

An angiographic study[1]

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In order to study left ventricular filling in hypertrophic cardiomyopathy, left ventricular cineangiograms of 20 patients were digitised frame by frame and compared with those of 10 normal subjects. Peak left ventricular filling rate was 770 ± 260 *ml* s^{-1} *(mean* ± 1 *standard deviation), not significantly different from normal. Mitral valve opening was delayed, occurring* 140 ± 40 *ms after time of minimum cavity area, compared with* 93 ± 14 *msec in normals* ($P < 0{\cdot}01$)*, indicating abnormal relaxation. Peak left ventricular filling rate was correlated inversely with this delay* ($r = 0{\cdot}69$, $P < 0{\cdot}01$)*, which was greater in patients with angina* (155 ± 27 *ms) than in those without* (85 ± 23 *ms)* ($P < 0{\cdot}01$)*. The rapid filling period was also abnormally prolonged in 8 patients. End-diastolic transverse dimension was normal* ($5{\cdot}3 \pm 0{\cdot}7$ *cm) but end-systolic dimension was reduced* ($2{\cdot}4 \pm 0{\cdot}4$ *cm)* ($P < 0{\cdot}01$) *because of abnormal cavity shape. Peak rate of change of dimension during filling* ($18{\cdot}7 \pm 5{\cdot}3$ *cm* s^{-1}) *was greater than normal* ($11{\cdot}3 \pm 3{\cdot}9$ *cm* s^{-1}) ($P < 0{\cdot}01$)*, and correlated with peak filling rate* ($r = 0{\cdot}82$, $P < 0{\cdot}001$)*. Thus, peak filling rate is normal in hypertrophic cardiomyopathy, but the filling pattern may be abnormal, apparently because of impaired relaxation and abnormal cavity shape rather than mechanical obstruction to inflow.*

A significant component of the overall impairment of cardiac function in hypertrophic cardiomyopathy appears to be the abnormal diastolic function of the left ventricle (Hansen *et al.*, 1962; Goodwin, 1974). It has been suggested that increased elastic stiffness of the myocardium may be associated with a reduced rate of filling (Oakley, 1971) and indirect evidence for this has been obtained from the left atrial pressure pulse (Stewart *et al.*, 1968) and from the mitral echogram (Moreyra *et al.*, 1969). On the other hand, ventriculographic studies in a small number of patients have shown filling rates are within the normal range (Holt *et al.*, 1969; Hammermeister and Warbasse, 1974).

It was the purpose of the present study to examine the left ventricular filling pattern in a larger series of patients with hypertrophic cardiomyopathy. Since the limitations of ventriculographic volume analysis are greater when the left ventricle is small and irregular in shape, we have also used other methods of investigating the filling pattern during diastole. An attempt was made to elucidate the mechanisms by which these volume changes were brought about, and the findings were correlated with the clinical features of the condition.

Patients and methods

Twenty patients, 13 of whom were men, were studied after a diagnosis of hypertrophic cardiomyopathy had been made on ventriculographic criteria (Braunwald *et al.*, 1964). Clinical details are given in Table 1. The case records were examined retrospectively, with particular reference to the occurrence of angina or dyspnoea on exertion, heart size on chest radiography, the degree of left ventricular hypertrophy on electrocardiogram, left ventricular end-diastolic pressure, the degree of outflow tract obstruction, and the presence or absence of significant mitral regurgitation. Only 1 patient had been taking propranolol, which was stopped 5 days before diastolic ventriculography.

A second group of 10 patients was also studied. These complained of chest pain, but no haemodynamic or angiocardiographic abnormality of the heart or coronary arteries was found. This group is referred to as 'normal' though it is recognised that

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Table 1 *Details of patients*

Case No.	*Age (y)*	*Sex*	*Symptoms*	*NYHA grading*	*Heart* rate*	*Heart size (transverse diameter) on chest radiograph (cm)*	*Degree of LVH on ECG*	*End diastolic pressure (mmHg)*	*Mitral regurgitation*	*Presence or absence of LV outflow tract gradient*	
										At rest	*After provocation†*
1	29	F	Dyspnoea; palpitation with chest pain	II	85	12·5	±	25	Nil	+	+
2	39	M	Syncope	III	85	15 5	+	15	Slight	0	+
3	46	M	Dyspnoea	I	65	18 0	+	30	Slight	0	+
4	57	M	Dyspnoea; angina	III	90	14·0	±	10	Slight	+	+
5	41	M	Dyspnoea; angina	II	80	13·5	+++	20	Nil	0	0
6	57	F	Dyspnoea; angina	II	73	14·0	+++	—	Nil	0	++
7	27	M	Episodic dyspnoea, dizziness, and chest pain	III	100	13 5	+	16	Nil	0	+
8	56	F	Dyspnoea	II	75	13·5	LBBB	30	Gross	+	+
9	31	M	Palpitation	I	85	16 0	++	—	Nil	0	++
10	54	F	Dyspnoea; angina	II	67	14 0	0	15	Moderate	0	+
11	12	M	Dyspnoea; angina	II	90	14 0	++	12	Moderate	+	+
12	53	M	Dyanpoea; angina	II	75	14·5	++	18	Nil	0	+
13	26	M	Dyspnoea; angina	II	92	16·5	+++	20	Nil	0	0
14	52	F	Dyspnoea; angina	II	75	15 5	++	28	Nil	0	+++
15	50	M	Dyspnoea, angina	III	87	15·0	+	17	Slight	0	0
16	62	F	Dyspnoea, angina	III	67	13·0	±	16	Nil	+	0
17	44	M	Dyspnoea, angina	III	63	14·0	+++	30	Nil	0	+
18	33	M	Dyspnoea; angina	III	73	18·0	+++	—	Slight	+	+
19	51	F	Dyspnoea; angina	III	75	12 5	0	—	Slight	0	+
20	40	M	Palpitation; angina	II	60	14 0	+++	22	Moderate	0	++

*Derived from cycle length.
†Provocation by amyl nitrite inhalation or by ventricular ectopics.

minor or hitherto undescribed abnormalities may have been present.

CARDIAC CATHETERISATION AND ANGIOCARDIOGRAPHY

The patients were studied fasting, and were premedicated with diazepam. Right and left heart catheterisation was performed, either using the Seldinger method from the right femoral artery and vein or a cut-down right antecubital fossa. Pressures were measured with a fluid-filled manometer system and referred to the mid-thorax. An injection of 35 to 50 ml Triosil was made into the left ventricle at 10 ml per second, and cine film exposed at 48 frames per second. Calibration was performed by means of a grid at mid-chest level. Ectopic and postectopic beats were not studied.

DIGITISATION

Left ventricular cineangiocardiograms were digitised using methods that have previously been described (Gibson and Brown, 1975a). Successive frames of the beat to be studied were projected on to the digitising table, starting at end-diastole, and the perimeter of the cavity was traced using a cursor, starting from the aortic root.

ANALYSIS OF DATA

Plots were made of cavity area, derived by numerical integration, cavity perimeter, and long axis, representing the distance from the mid-point of the aortic root to the furthest point on the cavity perimeter (Fig. 1). Estimates of cavity volume and its rate of change were made using an area-length formula, based on an ellipsoidal model for the left ventricle (Dodge *et al.*, 1966). Shape index[1] (Gibson and Brown, 1975b) was also plotted; this function, which is independent of cavity size, has a maximum value of 1 when the cavity outline is circular, and a minimum of zero when cavity obliteration occurs. Plots were also made of a transverse left ventricular dimension and its rate of change, approximately at the level of the mitral valve (Gibson and Brown, 1975a) (Fig. 2). From these curves the following information was derived for each patient:

(1) Left ventricular volumes

End-systolic and end-diastolic volumes were calculated and then the ejection fraction was derived in the usual way. The peak rate of increase of left ventricular volume during the rapid phase of ventricular filling was also measured, and the increase in volume during left atrial systole was expressed as a percentage of the total volume change during diastole.

(2) Left ventricular dimension

End-systolic and end-diastolic transverse left ventricular dimensions, above the level of the

[1] Shape index $=4\pi$ area/perimeter^2.

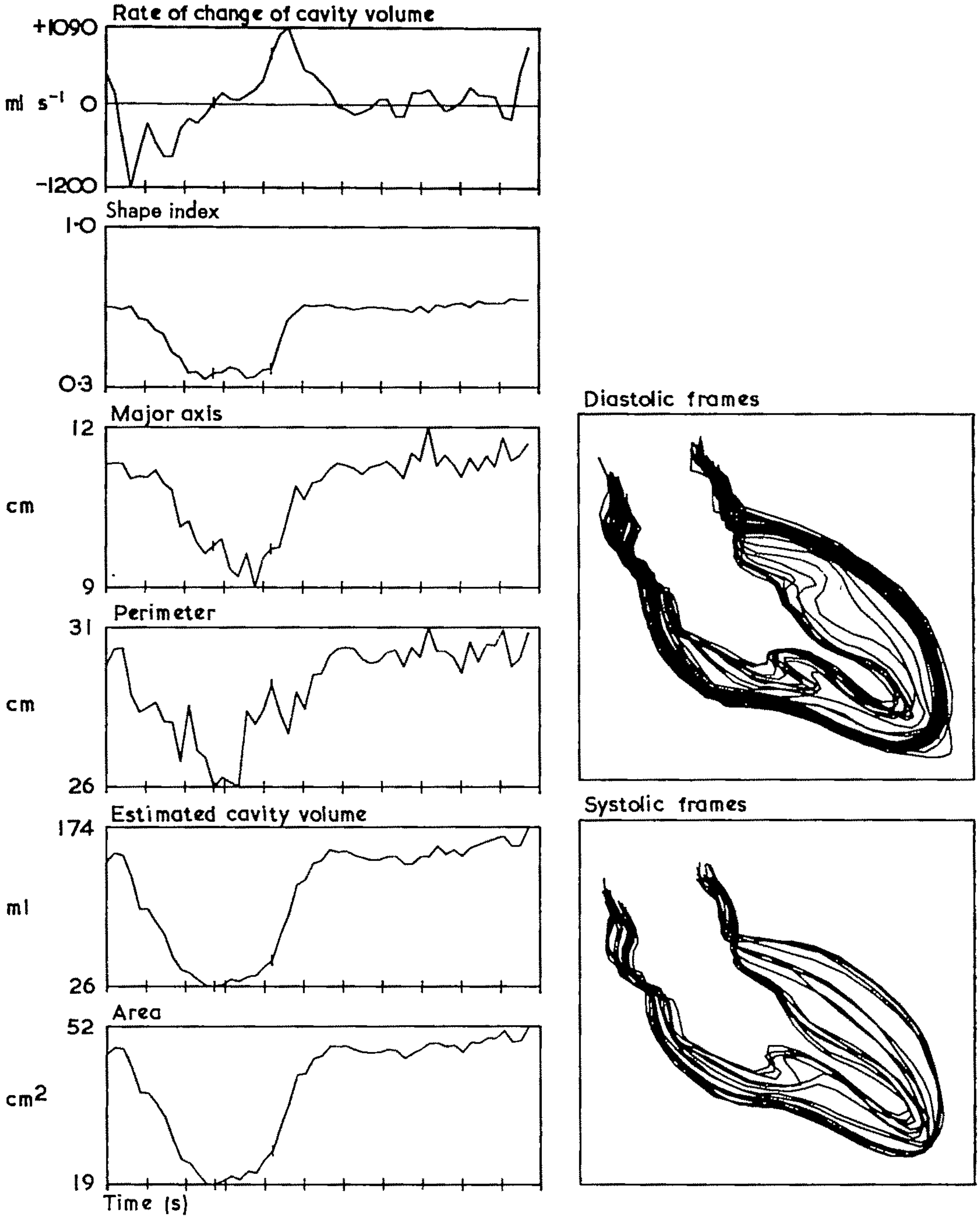

Fig. 1 *Plots of cavity area, long axis, perimeter, shape index, estimated cavity volume, and rate of change of volume. Vertical lines indicate minimum cavity area and mitral valve opening. Superimposed cavity outlines during systole (lower) and diastole (upper) are shown on the right (case 20, second beat).*

papillary muscles, and peak rate of change of dimension during early diastole were measured.

(3) Cavity configuration
End-systolic and end-diastolic shape indices were calculated, together with the change in shape index between the time of minimum cavity area and mitral valve opening.

(4) Diastolic time intervals
The time of minimum cavity area at end-ejection was identified. After this there is a slight increase in cavity area until the time of mitral valve opening (Ruttley *et al.*, 1974), taken as the frame in which unopacified blood from the left atrium first appears within the left ventricular cavity. The end of rapid filling could nearly always be identified as a clearly defined discontinuity on the curves of cavity volume and its rate of change with time (Straub, 1910). In the few patients in whom filling continued at an approximately constant rate until the end of the cardiac cycle with no recognisable period of diastasis, end-diastole was taken as the end of rapid filling.

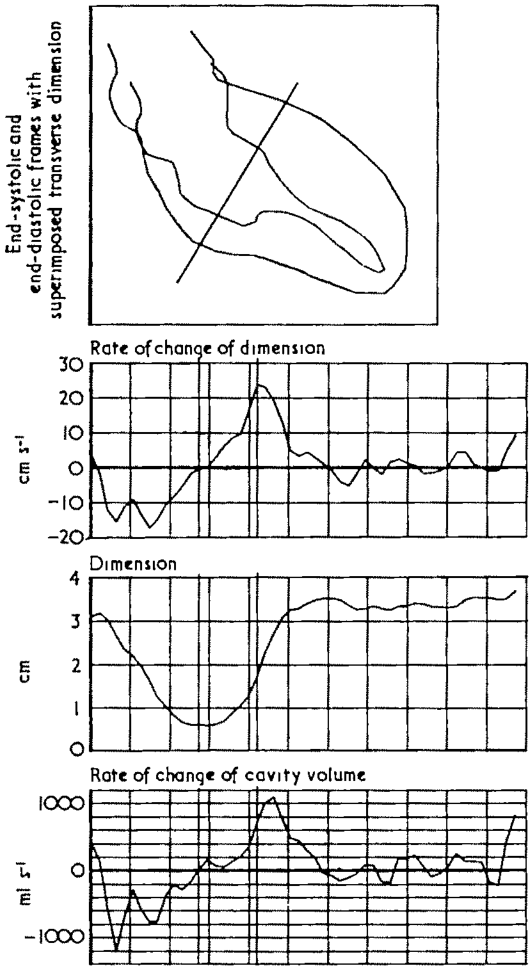

Fig. 2 *The uppermost plot shows the position of the chosen transverse dimension superimposed on the digitised outlines of the end-systolic and end-diastolic frames. Other plots show dimension, rate of change of dimension, and rate of change of estimated cavity volume (same patient as Fig. 1).*

Diastole could thus be subdivided into:
(i) The isovolumic relaxation time, from the time of minimum cavity area to mitral valve opening,
(ii) a period of rapid filling from mitral valve opening until the discontinuity on the volume curve, and
(iii) the period of diastasis and atrial systole.

The mean rate of rapid filling was calculated as the volume change between mitral valve opening and the discontinuity divided by the time interval between these two events.

OVERALL PATTERN OF WALL MOVEMENT

A general picture of left ventricular wall movement was obtained by superimposing cavity outlines, those from the start of the beat to the outline with the smallest area being taken as systolic, and the remainder as diastolic (Fig. 1). A more comprehensive display of wall movement was also used which was developed for the study of regional abnormalities occurring in ischaemic heart disease (Gibson *et al.*, 1976) (Fig. 3). Forty equally spaced points were identified on the end-diastolic cavity outline, starting from the mitral aspect of the aortic root and proceeding anti-clockwise. From each of these points, the nearest point on the end-systolic frame was sought. Wall movement was then plotted against time along each of the 40 lines thus defined. These plots were then stacked obliquely as an isometric display, with upward displacement on each representing inward movement. A series of lines joining simultaneous events were superimposed, those representing minimum cavity and mitral valve opening being accentuated. This display illustrates regional abnormalities of wall movement to, and their timing in, the cardiac cycle. From this display, the region of maximum outward wall movement during the period of isovolumic relaxation was identified, and its amplitude measured in the anterior and inferior regions of the ventricle.

Reproducibility
The reproducibility of the digitising technique for the analysis of cineangiograms has previously been

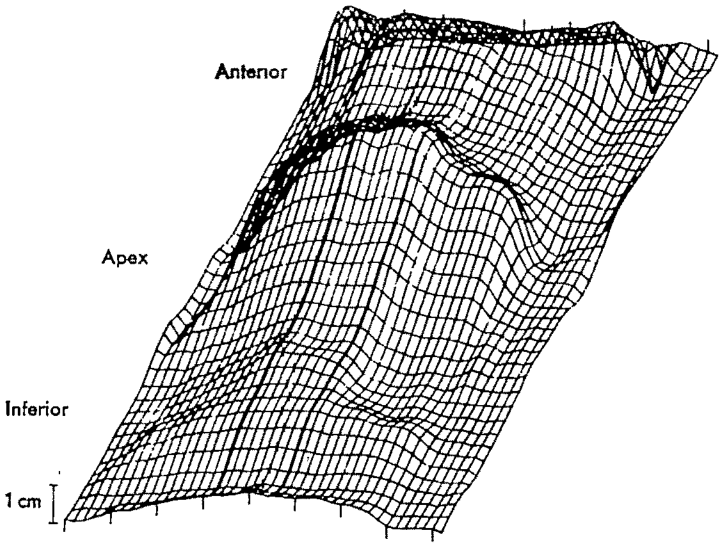

Fig. 3 *Plot of regional wall movement against time after the start of systole from the left ventriculogram (case 20). Each horizontal plot represents wall movement at one site around the perimeter of the cavity. Upward displacement represents inward movement. The diagonal lines are isochrones connecting events occurring simultaneously. The two accentuated isochrones show the times of minimum cavity area and mitral valve opening. 1 cm calibration is shown (bottom left).*

described (Gibson and Brown, 1975b). In view of the abnormal cavity shape, a separate assessment was made in the present study in 8 patients. Two consecutive beats and also two separate determinations of the same beat were analysed. The results are shown in Table 2, expressed as mean percentage error between pairs of observations.

Statistical methods

Student's t tests were used to assess the statistical significance of differences between means. Normal ranges are defined as a range of ±2 standard deviations about the corresponding mean of the normal group. Regression analysis was performed by the method of least squares.

Results

LEFT VENTRICULAR VOLUMES (Table 3)

Left ventricular end-diastolic and end-systolic volumes were within the normal range in all patients. There was considerable variation in peak rate of increase of volume during rapid filling, with a mean value for the group of 770 ± 260 ml s^{-1}, compared with the normal value of 610 ± 210 ml s^{-1}. When individual values were considered, the peak rate of increase of volume was greater than normal in 4 patients, all the remainder being within the normal range. Mean filling rate during early diastole was within the normal range in all except one patient with severe mitral regurgitation, in whom it was increased (1040 ml s^{-1}). In 8 patients in whom a separate atrial contribution was detectable, this amounted to 17 per cent (1 to 23%) of the total diastolic blood flow into the left ventricle.

LEFT VENTRICULAR DIMENSION (Table 4)

The mean end-diastolic dimension in the patients with hypertrophic cardiomyopathy was $5{\cdot}3\pm0{\cdot}7$ cm, not significantly different from normal, though values from the two patients with the largest end-diastolic volumes were outside the normal range. Mean end-systolic dimension was $2{\cdot}4\pm0{\cdot}4$ cm, significantly less than normal ($P<0{\cdot}01$). The peak rate of increase of dimension was $18{\cdot}5\pm5{\cdot}3$ cm s^{-1}, compared with the normal value of $11{\cdot}0\pm3{\cdot}9$ cm s^{-1}. In the patients with hypertrophic cardiomyopathy, there was significant correlation with peak rate of increase of volume, with the linear regression equation: peak rate of increase of volume $=41$ (peak rate of increase of dimension) $+8{\cdot}5$: $r=0{\cdot}82$; standard error of the estimate $=156$.

DIASTOLIC TIME INTERVALS

The mean isovolumic relaxation period in patients with hypertrophic cardiomyopathy was 140 ± 40 ms, significantly greater than normal (93 ± 14 ms) ($P<0{\cdot}01$). There was a negative correlation

Table 2 *Reproducibility studies (8 patients)*

	Mean percentage difference between repeat determinations	
	Same beat	*Consecutive beats*
Peak rate of increase of volume	10·3%	15·5%
End-diastolic volume	11·4%	12·5%
Isovolumic relaxation period	9·0%	5·0%
Rapid filling period	9·5%	9 0%

Table 3 *Analysis of cineangiograms*

Case No.	*Peak diastolic filling rate* (*ml* s^{-1})	*Mean diastolic filling rate* (*ml* s^{-1})	*EDV* (cm^3)	*EF* (%)	*IRP* (*ms*)	*Time to peak filling* (*ms*)	*RFP* (*ms*)	*Shape index*	
								End-systole	*End-diastole*
1	926	740	143	88	130	150	140	0·45	0·66
2	978	705	193	80	50	115	170	0·57	0·75
3	1213	700	174	80	90	105	130	0·45	0·64
4	1141	600	109	83	130	150	120	0·55	0·75
5	476	245	77	83	190	230	130	0·60	0·60
6	520	375	134	87	165	170	295	0·50	0·70
7	574	510	109	87	150	170	110	0·35	0·55
8	1302	1040	190	90	100	120	120	0·40	0·65
9	1008	800	132	81	100	130	110	0·35	0·55
10	699	480	136	88	140	180	190	0·40	0·70
11	640	615	164	88	120	150	210	0·35	0·55
12	750	520	146	83	170	240	180	0·45	0·65
13	873	630	131	82	130	170	130	0·40	0·55
14	659	415	150	81	210	350	250	0·40	0·60
15	579	325	68	83	160	230	125	0·40	0·58
16	543	365	82	92	125	200	130	0·42	0·65
17	383	230	93	83	200	—	210	0·45	0·55
18	620	455	199	88	150	200	250	0·40	0·60
19	584	400	115	82	150	170	165	0·55	0·63
20	978	700	156	80	145	170	125	0·40	0·65
HCM*	770 ±260	540 ±200	140 ±40	84 ±4	140 ±40	180 ±60	160 ±50	0·44 ±0·07	0·63 ±0·06
Normals*	610 ±210	460 ±170	120 ±40	80 ±6	93 ±14	150 ±40	130 ±20	0·65 ±0·03	0·84 ±0·04

EDV, end-diastolic volume; IRP, isovolumic relaxation period; HCM, hypertrophic cardiomyopathy; EF, ejection fraction; RFP, rapid filling period.
* = Mean values ±SD.

Table 4 *Analysis of transverse diameter*

	*End-systolic** (*cm*)	*End-diastolic** (*cm*)	*Peak diastolic rate of change** (*cm* s^{-1})	*Rapid filling period** (*ms*)
Hypertrophic cardiomyopathy	2·4 ±0·4	5·3 ±0·7	18·7 ±5·3	160 ±64
Normal	3·7 ±0·4	5·1 ±0·5	11·0 ±3·9	130 ±20

*Mean ±SD.

between isovolumic relaxation period and peak rate of increase of volume (r = −0·69, P < 0·01) (Fig. 4), and between isovolumic relaxation period and mean rate of increase of volume during the rapid filling period (r = −0·70, P < 0·01). The mean time from mitral valve opening to the end of the rapid filling period was 160 ±50 ms, estimated from the left ventricular volume record, compared with a normal value of 130 ±20 ms. The duration of the rapid filling period was also estimated from the transverse left ventricular dimension record as the interval between mitral valve opening and the discontinuity; this also gave a mean value of 160 ±65 ms.

CAVITY CONFIGURATION

The end-diastolic shape index had a mean value of 0·63 ±0·06, which was significantly less than normal, 0·85 ±0·04 (P < 0·001). The end-systolic value was 0·44 ±0·07 compared with a value of 0·65 ±0·03 in the normal group (P < 0·001). Representative displays of wall movement are given in Fig. 1 and 3. Mean outward wall movement during the isovolumic relaxation period was 4·7 ±2·8 mm along the anterior border and 3·6 ± 2·4 mm along the inferior. These values are not significantly different from normal. In no patient was inward wall movement observed during the isovolumic period, nor were localised abnormalities observed as in ischaemic heart disease (Gibson *et al.*, 1976). The mean shape index change during isovolumic relaxation (0·05 ±0·06) was also not significantly different from normal (0·06 ±0·02).

CLINICAL FEATURES

No relation was apparent between the pattern of left ventricular filling and the degree of dyspnoea, heart size on chest radiograph, the degree of left ventricular hypertrophy on electrocardiogram, end-diastolic pressure in the left ventricle, or the degree of outflow tract obstruction. Though the patient with the most rapid filling rate had mitral regurgitation, this was not a consistent relation in the group as a whole. There did, however, appear to be a strong association between the presence or absence of angina and the degree of diastolic

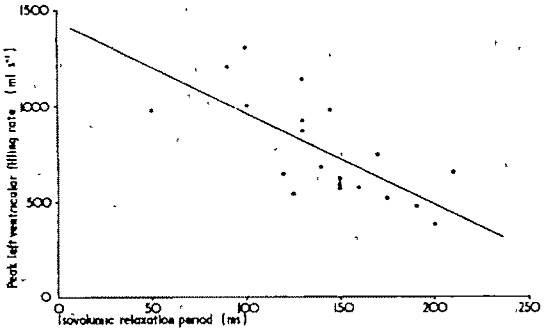

Fig. 4 *Relation between the isovolumic relaxation period and the peak diastolic filling rate. Simple linear regression line shown.*

abnormality. In patients with angina, isovolumic relaxation times were significantly longer than in those without, and peak filling rates were lower (Fig. 5 and 6).

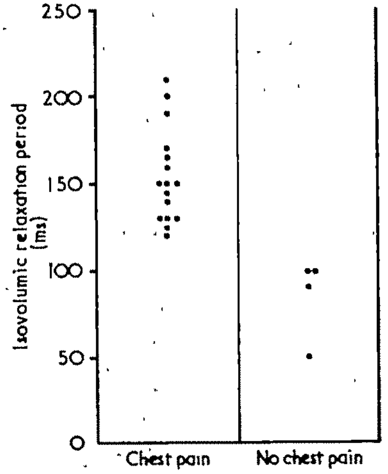

Fig. 5 *Relation between isovolumic relaxation period and presence of chest pain.*

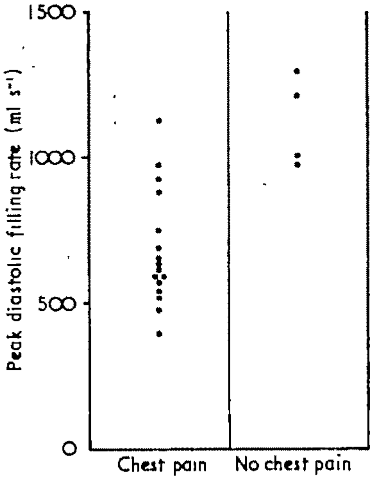

Fig. 6 *Relation between peak filling rate and presence of chest pain.*

Discussion

Measurement of left ventricular volume by angiography is subject to particular technical limitations in hypertrophic cardiomyopathy. The irregular shape of the cavity as outlined by radio-opaque dye is quite unlike any simple geometrical figure, and the trabeculations give it a ragged edge that cannot be completely digitised using the present method. A major problem in hypertrophic cardiomyopathy is presented by the hypertrophied papillary muscles. Though these occupy a significant part of the small cavity volume, with a corresponding reduction in the volume of blood contained in it, this is not reflected in angiographic estimates. More important, at end-diastole, the papillary muscles are within the cavity as defined by angiography, while at end-systole, they form its outer border. Thus, during early diastolic filling, there is a time when dye-containing blood first penetrates the space outside the papillary muscles, with a corresponding increase in projected area. Though this represents a true increase in cavity size, it is not associated with a corresponding amount of blood flow across the mitral valve. It is clear, therefore, that in patients with hypertrophic cardiomyopathy estimates of peak filling rates derived from left ventricular volume changes measured by angiography may be in error and, in particular, it is possible that peak rates of changes may represent movement of the papillary muscles rather than flow through the mitral valve. We have attempted to avoid these difficulties in two ways. The duration of the rapid filling phase can readily be measured in normal subjects and in the majority of patients with hypertrophic cardiomyopathy as the time interval between mitral valve opening and a discontinuity on the volume curve representing the onset of diastasis. This time interval was used to calculate the mean rate of increase of volume during rapid filling, which was shown both in normal subjects and in patients with hypertrophic cardiomyopathy to correlate closely with peak values. Secondly, it was possible to study the transverse dimension of the cavity at the level of the mitral valve, in a region of the ventricle above the papillary muscles, where trabeculation is less conspicuous. Peak rates of change of volume correlated closely with those of dimension, and estimates of the time of onset of diastasis made by the two methods were also very similar. It seems, therefore, that in spite of the very abnormal left ventricular cavity shape, measurement of either transverse dimension or volume can be used to assess filling pattern in hypertrophic cardiomyopathy. The same problems affect measurement of shape index which also depends on definition of the cavity perimeter. However, the effect of any smoothing introduced during the digitising process is to reduce the perimeter, thus overestimating shape index, particularly at end-systole, so that any error in the present study is towards underestimating the magnitude of changes in cavity shape during the cardiac cycle.

It is well documented that the properties of the left ventricular wall are abnormal in hypertrophic cardiomyopathy. End-diastolic pressure may be greatly increased in spite of a normal or even reduced end-diastolic volume. Increased passive elastic stiffness or reduced compliance have been reported, as might be anticipated on the basis of the very abnormal structure of the myocardium. It may seem surprising, therefore, that in spite of these abnormalities, early diastolic filling is able to proceed at a normal rate as was found in this study. In order to reconcile our results with these observations, it must be stressed that any description of the properties of the ventricle using terms such as compliance or elastic stiffness, presupposes that it is behaving in a static and passive manner (Mirsky, 1976) which is a very specific type of mechanical behaviour. There is no evidence to suggest that the ventricular wall does behave in this way during early diastole, and indeed there is much to the contrary. Ventricular volume increases while pressure is still dropping, a situation that is clearly not passive, as the properties of the ventricle are changing rapidly with time (Katz, 1930; Dodge *et al.,* 1962; Porter *et al.,* 1971). Similarly, in mid-diastole, transverse diameter can increase with little or no change in estimated wall stress (Gibson and Brown, 1974), suggesting that filling at this stage is mediated by reorientation rather than stretching of muscle fibres. One way in which this could occur is by a change in cavity shape towards a more spherical configuration. Only during late diastole does the ventricle show simple elastic behaviour, and only at this time, therefore, would the effects of abnormal wall stiffness become apparent. The results of the present study are compatible with these ideas. Left ventricular shape index in hypertrophic cardiomyopathy was significantly lower at end-diastole than in the normal group, and the change with systole was proportionately greater indicating that more of the inflow was accommodated by a change in cavity shape. The results thus support the idea of an altered mechanism of left ventricular filling in hypertrophic cardiomyopathy in which volume changes are mediated to a greater extent by changes in cavity shape, representing an adaptation to the increased stiffness of the myocardium. During atrial systole, when this mechanism does not operate, reduced ventricular compliance causes the increase in left ventricular volume to be within normal limits in spite of the large increase in end-diastolic pressure that may occur in these patients (Bruns, 1970; Hammermeister and Warbasse, 1974).

Other diastolic abnormalities in patients with hypertrophic cardiomyopathy have been defined in this study. The isovolumic relaxation time, defined as the interval between minimum cavity area and mitral valve opening, was found to be significantly prolonged. This probably reflects a reduced rate of fall of left ventricular pressure, since aortic or left atrial pressure would have had to be well outside the physiological range to have caused this abnormality. This prolongation of ventricular relaxation appears to be a primary abnormality in hypertrophic cardiomyopathy. It is likely to have caused the increase in time interval between aortic valve closure and the 'O' point of the apex cardiogram previously reported in a similar group of patients (Hubner *et al.,* 1973; Goodwin, 1974; Hardarson, 1974). However, the 'O' point may occur up to 150 ms after mitral valve opening, so that this interval also includes a significant part of the early rapid phase of ventricular filling (Prewitt *et al.,* 1975).

It has been suggested that left ventricular inflow tract obstruction may occur in hypertrophic cardiomyopathy, similar to that caused by mitral stenosis (Shabetai and Davidson, 1972; Feizi and Emanuel, 1975). Left ventricular filling in mitral stenosis differs from normal, not only in that the peak rate of increase of volume is reduced, but also in that the pattern of an early diastolic rapid filling phase followed by diastasis is lost and replaced by a lower rate of filling maintained for a longer period. In the present patients, peak rates of increase of volume were normal, but in 8 the duration of the rapid filling phase was prolonged beyond the upper limit of normal of 170 ms, so that the filling pattern did to some extent resemble that in mitral stenosis. Though it is possible that this prolonged rapid filling phase resulted from mechanical obstruction to inflow, its relation in individual patients to the delay in mitral valve opening (Fig.

4) suggests that it is already determined before filling starts, and is thus more likely to be a further manifestation of abnormal relaxation. The disturbances of function described here may be a reflection of the abnormal structure of the left ventricle in hypertrophic cardiomyopathy. Not only is the wall of the ventricle very considerably thickened, but also the usual arrangement of muscle fibres is disturbed to a variable extent by the presence of foci in which myocardial architecture is distorted by irregularly arranged bizarre muscle cells (Olsen, 1971; Van Noorden *et al.*, 1971; Ferrans *et al.*, 1972). It is thus possible that prolonged relaxation may occur in patients in whom these abnormal areas are more extensive, while increased wall stiffness may be a function of hypertrophy of normal myocardial cells, linearly arranged.

These early diastolic abnormalities in hypertrophic cardiomyopathy may be compared with those in ischaemic heart disease. Delayed mitral valve opening has also been observed in patients with ischaemic heart disease when it is frequently associated with complex changes in cavity shape during isovolumic relaxation related to the pattern of coronary arterial involvement (Gibson *et al.*, 1976). In contrast, delayed mitral valve opening in hypertrophic cardiomyopathy was found to be associated with uniform wall movement and was not accompanied by any significant change in cavity shape. The correlation between a prolonged relaxation period and a history of anginal pain was a suggestive one in our patients, and appeared sufficiently clear-cut to be significant in individuals. The greater part of coronary blood flow takes place in diastole (Gregg and Fisher, 1963), and only at this time in the subendocardial layers (Kirk and Honig, 1964). Prolonged isovolumic relaxation might be expected to reduce subendocardial blood flow, particularly when the duration of diastole is further reduced by tachycardia. The resemblance between events during isovolumic relaxation in patients with ischaemic heart disease and in those with hypertrophic cardiomyopathy raises the possibility that angina in the two conditions may have a similar basis.

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Cardiomegaly of unknown origin among Nigerian adults: role of hypertension in its aetiology

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Fifty Nigerians with cardiomegaly of unknown origin were followed up over a period of 1 to 4 years. This condition was defined as congestive cardiac failure and cardiac enlargement of unknown cause with a presenting diastolic blood pressure of not more than 100 mmHg. Twenty-four of the patients presented with a normal blood pressure (diastolic blood pressure below 90 mmHg) and 26 with a diastolic blood pressure of 90 to 100 mmHg. Each patient was initially treated in hospital with digoxin and frusemide and followed up as an out-patient. Of the 24 normotensive patients, 18 remained normotensive throughout the entire observation period. Heart failure was controlled with digoxin and frusemide both as an in-patient and in the subsequent out-patient follow-up. The heart failure of the remaining 6 patients was controlled in hospital but they developed high blood pressures and relapsed into heart failure during out-patient follow-up on digoxin and frusemide. They needed antihypertensive therapy in the form of thiazides or methyldopa and thiazides to keep them out of heart failure. Twenty patients with initially raised blood pressures responded to in-patient treatment with a fall in blood pressure and remission of their cardiac failure. During out-patient follow-up the blood pressure became raised again and cardiac failure reappeared. These patients also needed antihypertensive therapy to produce a sustained fall in blood pressure and relief of their heart failure. Six other patients who presented with raised blood pressures did not respond even as in-patients until antihypertensive therapy had been instituted.

It is concluded that not all Nigerians with cardiomegaly of unknown origin are hypertensives. The mild hypertension seen in some of the patients contributes to their morbidity and is not a result of their heart failure. Hypertension, however, is probably not the sole cause of their heart failure but acts in concert with other factors to produce their severe myocardial damage.

There have been various descriptions of the pathology, haemodynamics, clinical, radiological, and electrocardiographic features of cardiomegaly of unknown origin from different parts of the world (Reisinger and Blumenthal, 1941; Higginson *et al.*, 1952; Becker *et al.*, 1953; Brigden, 1957; Mattingly, 1961; Edington and Jackson, 1963; Stuart and Hayes, 1963; World Health Organization, 1965; Cockshott *et al.*, 1967; Edington and Hutt, 1968; Parry, 1968; Antia, 1968; Goodwin and Oakley, 1972; Goodwin, 1972a). One of the recognised features of this disease is a transient rise in diastolic blood pressure, the rise in pressure usually being limited to the period of congestive cardiac failure (Reisinger and Blumenthal, 1941; Brigden, 1957; Stuart and Hayes, 1963; Fowler, 1964; World Health Organization, 1965; Tobin *et al.*, 1967; Parry, 1968). With response to treatment of the heart failure, the diastolic pressure tends to return to normal. No other evidence of hypertension is found, apart from minor arterial changes in the ocular fundi (Parry, 1968). The transient rise in blood pressure also called reactive hypertension (Akinkugbe, 1972; Brockington, 1974) is usually regarded as secondary to heart failure, lasting as long as the heart is in failure, with the primary pathology being in the myocardium (Fishberg, 1940; Davies *et al.*, 1951; Fowler, 1964; Harvey *et al.*, 1964; Massumi *et al.*, 1965; Akinkugbe, 1972).

Oakley (1972) and Brockington (1972), however, recently suggested that cardiomegaly of unknown origin is a disguised variant of hypertensive heart disease, a view that was challenged by Goodwin (1972b). Later, Brockington (1974), in a comparative study of the epidemiology, clinical manifestations, pathology, and aortic diameters on chest radiographs of patients with hypertensive heart failure and cardiomegaly of unknown origin, came to the

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conclusion that the latter is a late stage of untreated hypertension.

At the University College Hospital, Ibadan, Nigeria, cardiomegaly of unknown origin, otherwise known as 'heart muscle disease', is the diagnosis most often made in adults presenting with heart failure, and it is the second cause of death from heart disease in our population (Brockington and Bohrer, 1970). Fifty Nigerians with cardiomegaly of unknown origin who were recently admitted to our wards afforded us the opportunity to study their natural history in some detail. This paper describes our findings in the evaluation of the role of hypertension in the aetiology of cardiomegaly of unknown origin.

Subjects and methods

The patients were diagnosed as suffering from cardiomegaly of unknown origin if they had congestive cardiac failure and cardiac enlargement confirmed by plain *x*-ray film of the chest, and if the known causes of heart failure or enlargement such as anaemia, congenital heart disease, organic valvular disease, endomyocardial fibrosis, and obstructive hypertrophic cardiomyopathy had been excluded on clinical grounds. They were unselected and constituted a consecutive series admitted either as emergencies or from the out-patient clinic.

Only patients with a presenting diastolic blood pressure of 100 mmHg and below were admitted to the study. Patients with higher diastolic blood pressures were diagnosed as having hypertensive heart failure.

Inquiries were made from each patient about alcohol ingestion, family illness, type of diet, annual income, and, where applicable, number of pregnancies. Further confirmation of the alcohol and family history was obtained in the majority of them from their relatives and friends. This was necessary because many of the patients were reluctant to disclose information about their family and sometimes told lies about their alcohol intake. Consumption of at least 2000 ml beer or palm-wine or 375 ml spirits daily for over 5 years was considered as a heavy and prolonged intake of alcohol. All the patients were classified into upper and lower socio-economic groups as defined by Osuntokun *et al.* (1971).

Each patient on admission was given digitalis and frusemide 80 mg daily. This dose of frusemide was increased up to 240 mg daily if there was no improvement. Frusemide was chosen because of its small antihypertensive effect when compared with thiazides (Anderson *et al.*, 1971). The patients were maintained on the same dose of drugs on discharge from hospital. Thiazides and when necessary methyldopa were substituted for frusemide if the blood pressure remained high.

On recovery from heart failure, 20 of the patients (12 men and 8 women) were readmitted and observed on maintenance digoxin alone. Each of them was allowed liberal use of salt in his food. Their blood pressures and pulse rates were carefully monitored daily. The original treatment was resumed when they relapsed into heart failure. Blood pressures were recorded in the supine position after 3 minutes of rest using a mercury sphygmomanometer. The first and the fifth Korotkoff sounds were used as measures of systolic and diastolic blood pressures. Blood pressures were recorded by the author only, in order to eliminate observer variation.

All the patients had chest *x*-ray examinations, electrocardiograms, erythrocyte sedimentation rates, urinalyses, haemoglobin and packed cell volume estimations, leucocyte counts, electrolyte and urea analyses, serum protein analyses, and liver function tests. Of the 50 patients, 33 had cardiac catheterisation and angiography. All the patients were followed up for periods ranging from 1 year to 4 years.

Results

The 50 patients were made up of 28 women and 22 men. Their age and sex distribution is shown in Fig. 1.

PRESENTING BLOOD PRESSURE

Of the 50 patients, 24 (group A) presented with diastolic blood pressures below 90 mmHg. The remaining 26 patients (group B) presented with diastolic blood pressures between 90 mmHg and 100 mmHg. Their presenting systolic pressures are shown in Table 1.

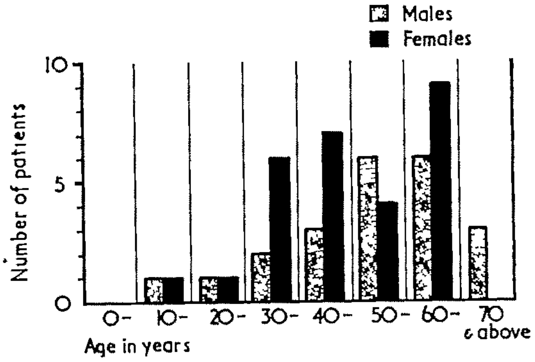

Fig. 1 *Age and sex distribution of the 50 patients*

Table 1 *Presenting systolic pressures in 50 patients*

Systolic blood pressure (mmHg)	*No. of patients*
100 and below	4
101–110	11
111–120	8
121–130	16
131–140	7
141–150	1
151–160	3

CLINICAL COURSE

Group A

Eighteen (Group A1; Table 2) of these patients remained normotensive on digoxin and frusemide both as in-patients and out-patients. The remaining 6 patients (group A2; Table 3) on admission responded similarly to digitalis and frusemide but as out-patients relapsed on these drugs into congestive cardiac failure with raised blood pressures. They subsequently improved when their diuretics were changed to thiazides. One of them (case 22) also required methyldopa to keep him out of heart failure.

Group B

Twenty (group B1; Table 4) of the patients in this group improved on digitalis and frusemide as in-patients. Their diastolic blood pressures returned to normal within a week. However, on discharge from hospital and on the same dose of drugs as at discharge, they relapsed into heart failure with raised

Table 2 *Summary of clinical course of patients in group A1, on digoxin and frusemide as in-patients and at first visit as out-patients*

Case No.	*Findings at admission*				*In-patient findings just before discharge*				*First visit as out-patient*				*Remarks*
	CCF	*Apical PSM*	*3rd sound*	*BP (mmHg)*	*CCF*	*Apical PSM*	*3rd sound*	*BP (mmHg)*	*CCF*	*Apical PSM*	*3rd sound*	*BP (mmHg)*	
1	+	—	+	120/80	—	—	+	120/80	—	—	+	100/60	Subsequently developed tricuspid regurgitation
2	+	+	+	110/70	—	—	—	110/70	—	—	—	120/75	
3	+	—	+	90/55	—	—	+	100/60	—	—	+	100/60	Tricuspid regurgitation also
4	+	+	+	130/80	—	+	+	125/85	—	—	+	120/80	Tricuspid regurgitation also
5	+	+	+	110/70	—	+	—	110/75	—	+	—	120/70	
6	+	—	+	120/80	—	—	—	100/60	—	—	—	110/70	
7	+	+	+	110/80	—	—	—	130/85	—	—	—	120/80	
8	+	+	+	120/85	—	+	+	120/80	—	+	+	110/70	
9	+	—	+	110/70	—	—	+	110/80	—	—	+	120/75	
10	+	—	+	100/70	—	—	+	110/75	—	—	+	110/70	Later developed tricuspid regurgitation
11	+	+	+	110/65	—	+	+	110/60	—	+	+	110/75	Tricuspid regurgitation also
12	+	—	+	130/70	—	—	+	110/70	—	—	+	120/80	Tricuspid regurgitation also
13	+	+	+	120/80	—	+	+	110/70	—	+	+	120/80	Tricuspid regurgitation also
14	+	+	+	130/80	—	+	+	120/75	—	+	+	120/70	
15	+	+	+	125/85	—	+	+	110/70	—	+	+	120/70	
16	+	+	+	90/70	—	+	+	190/75	—	+	+	100/60	
17	+	+	+	110/85	—	+	+	120/80	—	+	+	120/80	
18	+	+	+	95/60	—	+	+	100/60	—	+	+	100/60	

CCF, congestive cardiac failure, PSM, pansystolic murmur; BP, blood pressure.

Table 3 *Summary of clinical course of patients in group A2, on digoxin and frusemide as in-patients and at first visit as out-patients*

Case No.	*Findings at admission*				*In-patient findings just before discharge*				*First visit as out-patient*				*Remarks*
	CCF	*Apical PSM*	*3rd sound*	*BP (mmHg)*	*CCF*	*Apical PSM*	*3rd sound*	*BP (mmHg)*	*CCF*	*Apical PSM*	*3rd sound*	*BP (mmHg)*	
19	+	+	+	105/70	—	—	—	110/80	+	+	+	130/100	Improved on thiazides
20	+	+	+	110/70	—	—	—	100/80	+	—	+	140/105	Improved on thiazides
21	+	+	+	140/80	—	—	—	130/80	+	—	+	160/100	Improved on thiazides
22	+	+	+	120/85	—	—	—	120/75	+	—	+	150/110	Improved on methyldopa and thiazides
23	+	—	+	120/80	—	—	—	120/80	+	—	+	130/115	Improved on thiazides
24	+	+	+	110/80	—	—	+	100/80	+	+	+	130/100	Improved on thiazides

Table 4 *Summary of clinical course of patients in group B1 on same dose of digoxin and frusemide as in-patients and as out-patients*

Case No.	*Findings at admission*				*In-patient findings just before discharge*				*First visit as out-patient*				*Remarks*
	CCF	*Apical PSM*	*3rd sound*	*BP (mmHg)*	*CCF*	*Apical PSM*	*3rd sound*	*BP (mmHg)*	*CCF*	*Apical PSM*	*3rd sound*	*BP (mmHg)*	
25	+	+	+	135/90	—	+	+	110/80	+	+	+	120/100	Improved on thiazides
26	+	+	+	130/90	—	—	—	110/70	+	+	+	150/105	Improved on thiazides
27	+	+	+	130/95	—	—	—	120/80	+	+	+	140/100	Improved on thiazides
28	+	+	+	160/90	—	—	—	120/80	+	+	+	170/100	Improved on thiazides
29	+	+	+	110/90	—	—	—	100/70	+	+	+	120/100	Improved on thiazides
30	+	+	+	130/90	—	—	—	115/75	+	—	+	170/100	Improved on thiazides
31	+	+	+	130/90	—	—	—	110/80	+	+	+	130/95	Improved on thiazides
32	+	—	+	145/100	—	—	—	130/80	+	+	+	140/105	Improved on methyldopa and thiazides
33	+	+	+	125/100	—	+	+	120/80	+	+	+	140/105	Improved on methyldopa and thiazides
34	+	+	+	140/100	—	—	—	120/70	+	+	+	140/105	Improved on thiazides
35	+	+	+	110/100	—	—	—	130/80	+	+	+	140/100	Improved on thiazides, had tricuspid regurgitation also
36	+	+	+	135/100	—	—	—	120/70	+	—	+	210/110	Improved on methyldopa and thiazides
37	+	—	+	140/100	—	—	+	120/80	+	—	+	150/110	Improved on methyldopa and thiazides
38	+	+	+	120/100	—	—	—	105/85	+	+	+	120/100	Improved on thiazides
39	+	—	+	120/100	—	—	—	105/80	—	—	+	135/105	Improved on thiazides
40	+	—	+	160/100	—	—	—	150/80	+	—	+	170/100	Improved on thiazides
41	+	—	+	140/100	—	—	—	120/70	+	—	+	170/105	Improved on thiazides
42	+	+	+	130/100	—	—	+	100/60	+	+	+	170/95	Improved on thiazides; had tricuspid regurgitation in addition
43	+	+	+	130/90	—	—	+	120/80	+	+	+	140/100	Improved on thiazides
44	+	+	+	120/100	—	—	+	130/80	+	+	+	140/110	Improved on thiazides

CCF, congestive cardiac failure, PSM, pansystolic murmur; BP, blood pressure.

Table 5 *Summary of clinical course of patients in group B2*

Case No.	*Findings at admission*				*In-patient treatment (1)*				*(2)*				*Out-patient (3)*			
	CCF	*Apical PSM*	*3rd sound*	*BP (mmHg)*	*CCF*	*Apical PSM*	*3rd sound*	*BP (mmHg)*	*CCF*	*Apical PSM*	*3rd sound*	*BP (mmHg)*	*CCF*	*Apical PSM*	*3rd sound*	*BP (mmHg)*
45	+	+	+	130/100	+	—	+	130/105	—	—	—	120/85	—	—	—	120/80
46	+	—	+	160/90	+	—	+	150/105	—	—	—	170/75	—	—	—	150/70
47	+	—	+	130/95	+	+	+	170/100	—	+	+	140/85	—	—	+	150/95
48	+	+	+	140/100	+	—	—	140/100	—	—	—	110/75	—	—	—	150/80
49	+	—	+	130/100	+	+	+	150/110	—	+	+	120/85	—	—	+	120/100
50	+	—	+	130/100	+	—	—	140/105	—	—	—	110/80	—	—	—	130/85

(1) Response to digoxin and frusemide; (2) Response to thiazides (case 45) or alpha methyldopa and thiazides (remaining patients); (3) Subsequent reponse as out-patients; patients were on the same drugs as in (2).
CCF, congestive cardiac failure, PSM, pansystolic murmur; BP, blood pressure.

blood pressures. Of the 20 patients, 16 subsequently improved when their diuretics were changed to thiazides. The remaining 4 patients required methyldopa in addition to thiazides to improve their heart failure. These 4 patients subsequently remained well on these drugs without added digoxin.

The remaining 6 patients (group B2; Table 5) in group B showed no response to digoxin and frusemide as in-patients. Their diastolic blood pressures remained persistently raised throughout the period they were in failure. One of them improved when his diuretic was changed to hydrochlorothiazide. The other 5 patients required methyldopa in addition to thiazide diuretics to improve their heart failure.

PATIENTS ON DIGOXIN WITHOUT DIURETICS

Fig. 2a and 2b show the behaviour of the blood pressures of 20 patients, who after recovery were readmitted to hospital and observed on digoxin alone, with no salt restriction. Eight of them were

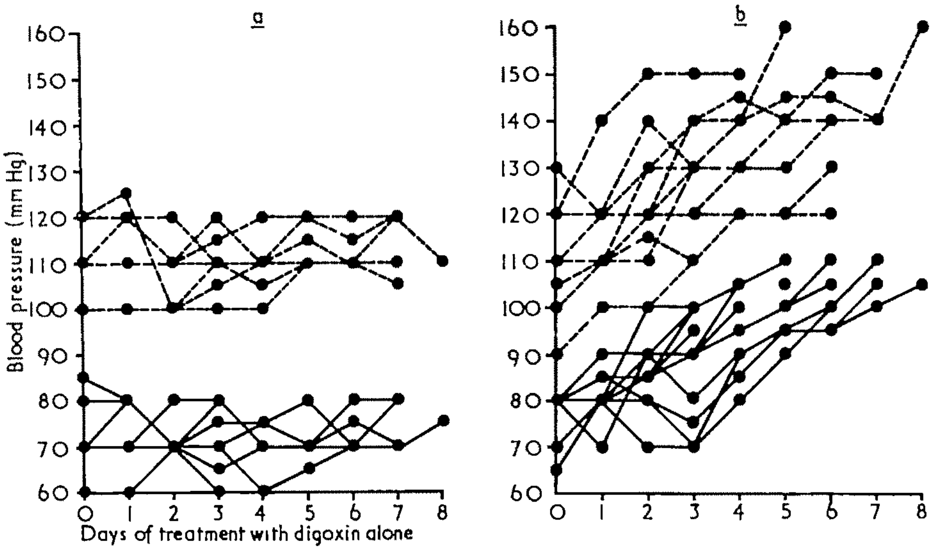

Fig. 2 *(a) Behaviour of the blood pressures of 8 patients who were normotensive throughout. (b) 12 patients who responded with mild hypertension to digoxin alone without diuretics or restricted salt intake.*

from group A1, 2 from group A2, 8 from group B1, and 2 from group B2. They had all previously been seen as in-patients, then discharged, and observed for varying periods as out-patients before their readmission.

All the 20 patients had symptoms of heart failure between the fourth and the seventh day of readmission. The 8 patients in group A1 however had no previous rise in blood pressure before they had symptoms of heart failure (Fig. 2a). The remaining 12 patients on the other hand had an initial rise in blood pressure (Fig. 2b). The following is an illustrative case report.

Case report

A woman of 50 years was admitted 3 months previously in congestive heart failure with mitral regurgitation and a loud third sound. Her blood pressure then was 140/100 mmHg. She subsequently improved on digoxin and hydrochlorothiazide (100 mg daily). At the time of her second admission, she was free of heart failure, her blood pressure was 120/80 mmHg, she had no third heart sound, and no apical systolic murmur. Her hydrochlorothiazide was then stopped and she was allowed liberal use of salt.

Three days afterwards, her blood pressure was 120/95 mmHg, and a fourth sound was heard at the apex together with a soft midsystolic murmur. Two days after this, her blood pressure was 140/100 mmHg, her systolic murmur was louder, and both third and fourth sounds were audible. Seven days after her diuretics were stopped, she complained of dyspnoea. Her blood pressure was 150/110 mmHg, her jugular venous pressure was raised and a loud third heart sound together with a midsystolic murmur were heard at the apex. Her pulmonary closure sound was louder but she had no crepitations in the chest. She subsequently improved when hydrochlorothiazide (100 mg daily) was again started.

CLINICAL FEATURES

All the 50 patients were admitted in congestive heart failure. Symptoms of left heart failure predominated. The duration of symptoms ranged between 2 and 84 months with a mean of 11 months. Twenty-seven (54%) of them gave a history of chest pain at onset of illness. In 16 of these, the chest pain was a vague discomfort not typically anginal. The remaining 11 had a pleuritic type of chest pain. Twenty patients (40%) volunteered a history of febrile illness before the onset of their symptoms. Seventeen patients (34%) had paraesthesiae.

One patient had been treated for heart failure 11 years previously. She received only digoxin at the time and improved subsequently. Thirteen patients (26%) belonged to the high socioeconomic group.

DIET

The diet of patients from the low socioeconomic group consisted largely of carbohydrates with low protein and fat content. The diet of the higher socioeconomic group resembled those in the lower socioeconomic group but with more animal protein and animal fat.

ALCOHOL

Twenty (40%) of the patients (16 men and 4 women) gave a history of excessive and prolonged intake of alcohol; 14 of them required thiazide diuretics or, in addition, methyldopa to keep them out of heart failure. The remaining 6 patients were normotensive as in-patients and out-patients. All the 13 patients who belonged to the high socioeconomic group in this study misused alcohol. The patients in the low socioeconomic group consumed mainly locally-brewed alcoholic beverages which were cheaper, easily obtainable, but nonstandardised. Those in the high socioeconomic group consumed mainly imported alcoholic beverages (beer, wine, spirits) though some of them misused locally brewed alcoholic drinks as well.

PARITY

Twenty (71%) of the 28 female patients have had 5 pregnancies or more. One had never been pregnant. Only 1 patient had symptoms of heart failure within 6 months of delivery.

FAMILY HISTORY

Two patients had strong family histories of hypertension. One other female patient had a husband who was hypertensive and both of them drank alcohol excessively.

NUTRITIONAL STATUS

Thirty-three (66%) patients had a poor nutritional status on clinical grounds. Of these, 16 were alcoholics.

FEVER

Only 1 patient was febrile on admission. He was found to have an acute exacerbation of chronic bronchitis. He had smoked cigarettes excessively for over 10 years and drank alcohol heavily too.

ARRHYTHMIA

All the patients were in sinus rhythm on admission. Eight of them had multifocal ventricular ectopics. These ectopics were presumed to be induced by digitalis in 2 patients; 3 others were alcoholics.

MURMURS

Thirty-four (68%) patients had apical pansystolic murmurs of mitral regurgitation on admission. This murmur persisted in only 17 patients after successful treatment. Of the 34 patients with mitral regurgitation, 7 had tricuspid regurgitation in addition. The latter, however, disappeared with recovery, except in 2 patients. Two other patients who had no regurgitation of the tricuspid valve on admission later developed this on follow-up. All the patients had a third sound.

OPTIC FUNDI

Five of the patients had grade I changes according to the Wagener and Keith classification (1939).

OTHER FINDINGS

Three patients had evidence of renal disease. One had non-functioning kidneys on intravenous pyelography. The second patient had bilateral small kidneys while the third died and was found at necropsy to have bilateral contracted granular kidneys consistent with arteriolonephrosclerosis.

Ten patients had Hb genotype AS. One other patient had Hb genotype AC; the rest were AA.

Two patients had cerebrovascular accidents thought to be embolic. Both of them recovered though they had residual hemipareses.

Discussion

The concept of reactive hypertension, 'Sahli's Hochdruckstauung' (Akinkugbe, 1972; Brockington, 1974), regarded as a feature of cardiomegaly of unknown origin implies a rise in blood pressure as a result of heart failure. It is well recognised that there is increased catecholamine secretion and sodium retention in heart failure (Oram, 1971); these are factors that tend to raise the blood pressure. However, a rise of blood pressure in heart failure occurs more often and in a more pronounced way in primary myocardial disease (Massumi *et al.*, 1965; Brockington, 1972).

Oakley (1972) and Brockington (1972) recently proposed that cardiomegaly of unknown origin is really hypertensive heart failure in disguise. They pointed out that a failing left ventricle cannot achieve an increase in mean blood pressure and that there are well documented hypertensives who lose the need for hypotensive drugs as their hearts get larger and fail. Brockington (1974) also compared the epidemiology, clinical picture, course, and pathology of cardiomegaly of unknown origin in Nigerians with hypertensive heart failure and found that they were similar except that cardiomegaly of unknown origin was more resistant to treatment.

Goodwin (1972b) on the other hand showed that the heart in hypertensive heart disease was different structurally from the heart in cardiomegaly of unknown origin. The heart in the former is more hypertrophied than dilated while that of the latter shows more cavity dilatation than hypertrophy. He also showed that while coronary artery disease was common in hypertension, it was rare in cardiomegaly of unknown origin. The electrocardiograms of the two diseases are different and the phase of hyperfunction or hypertrophy described by Meerson (1962) in his experimental work on cardiac hypertrophy is not seen in cardiomegaly of unknown origin.

There is little agreement at what level hypertension can be considered the cause of, rather than a consequence of myocardial failure (Brigden, 1957; Massumi *et al.*, 1965; World Health Organization, 1965; Brockington, 1974). At Ibadan, considerable difficulty often exists in separating cardiomegaly of unknown origin from hypertensive heart failure which is also common (Akinkugbe, 1972). Therefore, in this study an arbitrary diastolic level of 100 mmHg and below was chosen as compatible with cardiomegaly of unknown origin.

The patients in this study can broadly be divided into two groups. Both groups responded to routine management of heart failure on admission with frusemide as the diuretic. However, on discharge, with the therapy unchanged, the first group continued to do well while the second group relapsed with raised blood pressure; they improved only when the diuretic was changed to a thiazide.

The results show that not all Nigerians with cardiomegaly of unknown origin have raised blood pressure when they are in heart failure. They also show that the clinical course of the patients who are normotensive when in heart failure is different from those with mild hypertension. If hypertension is a consequence of their heart failure, it is difficult to explain why all the patients did not present with mildly raised blood pressures and why their clinical course was different. It seems more likely that the hypertension was contributing to the morbidity of the patients in the second group and the improvement in their heart failure was consequent on the lowering of their blood pressure. The factors which lowered their blood pressure in hospital were bed rest, low salt diet, and frusemide. As out-patients, because of the unrestricted activity and salt intake and the lack of effective control of their blood pressure by frusemide, their condition worsened. They, however, improved when a thiazide diuretic, a more effective hypotensive (Anderson *et al.*, 1971), was substituted. Such patients if treated with thiazides initially and as out-patients, may continue to maintain normal blood pressures and remain out of heart failure. If, however, the diuretic is discontinued, a rise in blood pressure may occur tilting them into heart failure (Falase, unpublished observations). This, we believe, explains why the hypertension in cardiomegaly of unknown origin is transient, occurs only when the patient is in heart failure, and improves with treatment. The fact that some of the patients required methyldopa, a known hypotensive, to improve the heart failure and that the 12 patients observed on digoxin alone after recovery from heart failure showed an initial rise in blood pressures before they had symptoms of heart failure, strongly suggest that these patients are hypertensives.

As shown at angiography (Fig. 3) and in the single case who died, the hearts of these patients showed more cavity dilatation than hypertrophy. These are not the typical hearts seen in hypertension (Goodwin, 1972b). In a recent necropsy study at Ibadan, however, it was observed that large flabby hearts were not restricted to cardiomegaly of unknown origin but could occur in established hypertensive heart disease (Attah and Falase, 1977).

In the present study, 14 hypertensive and 6 normotensive patients were alcoholics. Of the 28 female patients, 20 (71%) were multiparous. Only 1 had symptoms of heart failure within 6 months of delivery confirming the observation that postpartum cardiac failure is less common in the southern part of Nigeria than in the northern part (Ladipo, 1976). Alcohol, however, is known to cause myocardial disease (Brigden and Robinson, 1964; Burch and De Pasquale, 1968). Hypertension, therefore, may have two possible roles in causing the heart disease of patients with cardiomegaly of unknown origin. They may be long-standing hypertensives as suggested by Brockington (1974). Myocardial hypertrophy as a result of hypertension produces an imbalance between oxygen supply and demand causing myocardial hypoxia (Ibrahim and Tarazi, 1975). Such anoxic fibres may be more susceptible to alcohol and other injurious factors. The heart of a long-standing hypertensive who also consumed alcohol excessively, therefore, may, at a stage from repeated damage, become unable to withstand the afterload and, therefore, fails. Blood pressure then drops as a result of loss of myocardial function as postulated by Oakley (1972) and Brockington (1972). This may explain why the presenting blood pressure is low. On the other hand, these patients might have already had myocardial damage produced by these injurious factors but remain compensated. If they then develop hypertension, the hearts become unable to withstand the afterload, and failure supervenes at a relatively low level of diastolic blood pressure. Unfortunately, the premorbid pressures of our patients are not known and as such it is difficult to know which mechanism is operative.

In conclusion, not all Nigerians with cardio-

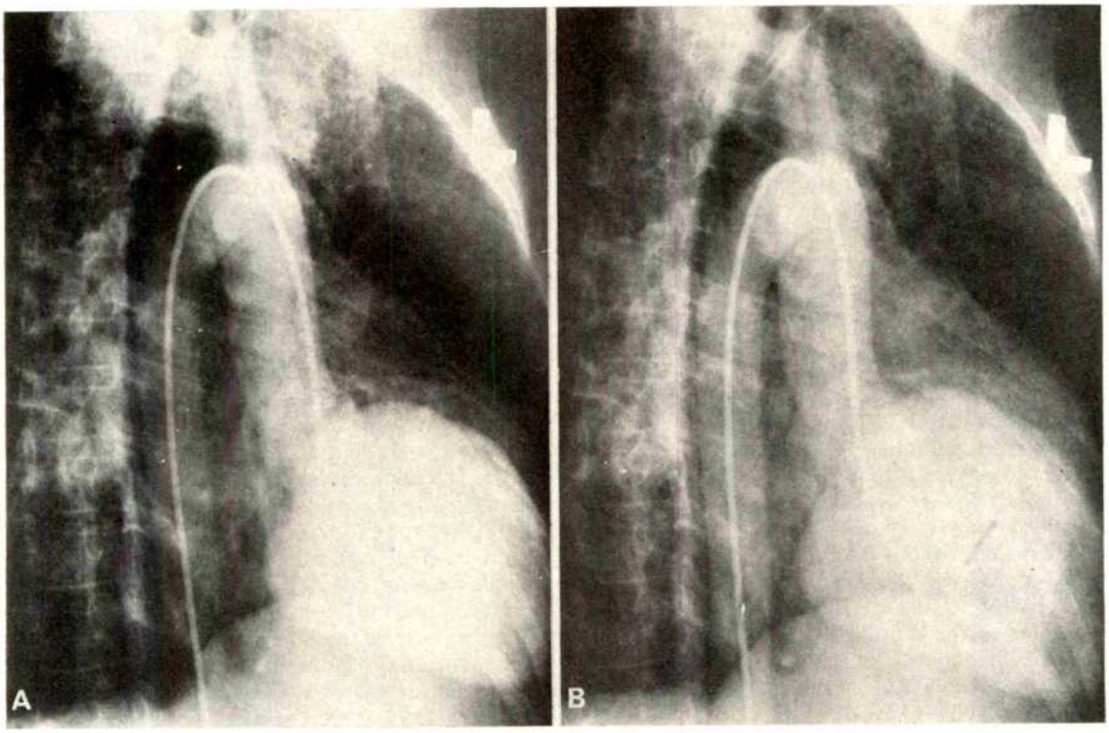

Fig. 3 *Left ventriculogram of case 39. Films taken during systole (A) and diastole (B) showing a dilated, poorly contractile left ventricle.*

megaly of unknown origin are hypertensives. The mild hypertension seen in some of the patients probably contributes to their morbidity and is not a result of their heart failure. They, however, have a greater degree of myocardial damage compared with other hypertensives. Thus, it may not be true to regard hypertension as the sole cause of their heart failure. Hypertension may be acting together with other factors such as alcohol to produce the severe myocardial damage seen in cardiomegaly of unknown origin.

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Case reports

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Dissimilar atrial rhythms[1]

A patient with interatrial block

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A patient with type A Wolff-Parkinson-White syndrome and prolonged interatrial conduction intervals developed atrial flutter during the course of an electrophysiological study. The atrial flutter blocked along the left-to-right conduction pathways in a Wenckebach pattern. The dissimilar atrial rhythms of right atrial tachycardia and left atrial flutter evolved as the interatrial block increased to 2:1 conduction.

Dissimilar atrial rhythms in man have been reported infrequently since Schrumpf's first description (Schrumpf, 1920). The forms of dissimilar atrial rhythms reported to date include dissociated regular rhythms of each atrium (Schrumpf, 1920; Bay and Adams, 1932; Scherf, 1955; Marques, 1958; Abarquez and La Due, 1961; Cohen and Scherf, 1965; Chung, 1971; Sivertssen and Jörgensen, 1973; Clark and Douglas, 1973; Scott and Finnegan, 1975), sinus rhythm with a segment of the atria in tachycardia (Chung, 1971), flutter (Chung, 1971; Dayem *et al.*, 1972), or fibrillation (Cohen and Scherf, 1965; Chung, 1969, 1971), and a rapid regular rhythm (tachycardia or flutter) of one atrium with simultaneous fibrillation of the other atrium (Zipes and Dejoseph, 1973; Leier and Schaal, 1975). Atrial standstill with flutter in another segment of the atria has also been reported to occur in man (Zipes and Dejoseph, 1973; Leier and Schaal, 1975; Wu *et al.*, 1975). We report a patient with left atrial flutter and right atrial tachycardia which occurred in the setting of 2:1 interatrial block and interatrial Wenckebach block.

Case report

The patient was a 66-year-old man with type A Wolff-Parkinson-White (WPW) syndrome and a 60-year history of intermittent tachycardia. Self-administered carotid massage consistently interrupted the tachyarrhythmia. Over the preceding 5 years, the episodes of tachycardia had increased in frequency and duration and were frequently accompanied by shortness of breath. No abnormality was found on physical examination. The electrocardiogram showed type A WPW pre-excitation. Other laboratory tests gave normal results.

Methods

A bipolar catheter was placed in the oesophagus for recording left atrial activity. Two bipolar catheters were placed in the high right atrium, one for right atrial pacing and the other for recording a high right atrial electrogram. A six-pole catheter was placed across the tricuspid valve for bundle of His and low right atrial recordings. Standard leads I, II, III, left atrial, and intracavitary right heart electrograms were recorded simultaneously on a multichannel oscilloscopic recorder (Electronics for Medicine DR-12) at paper speeds of 50 and 100 mm/s. Electrical stimuli (2 × threshold, 2 ms duration) were introduced by a pulse stimulator (Grass Instrument Model S 88, Quincy, Massachusetts).

Results

Baseline electrophysiological data obtained included a high to low right atrium conduction interval of 40 ms (normal <48 ms—Leier *et al.*, 1976), a prolonged right to left atrial conduction interval of 70 ms (normal <60 ms—Leier *et al.*, 1976), an AH interval of 90 ms, and an HV interval (to onset of delta wave) measuring 16 ms. Sinoatrial conduction times and corrected sinoatrial recovery times were found to be normal at 110 to 125 ms and 110 to 150 ms, respectively (Engel *et al.*, 1976). The effective refractory periods of the atrioventricular node and of the accessory pathway in sinus rhythm

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were 260 ms and 280 ms, respectively. The high to low right atrium and the right to left atrial conduction times increased above baseline values with atrial pacing (up to pacing rates of 160/min) and with atrial premature stimuli, but these manoeuvres did not elicit atrial Wenckebach block or any other form of intra- or interatrial block.

Placement of an atrial premature stimulus in the right atrium at an A_1-S_1 interval of 280 ms consistently initiated an episode of supraventricular tachycardia with atrial and ventricular rates of 136/min. These episodes were terminated with placement of an atrial premature stimulus in the right atrium at an A_1-S_1 interval of 250 ms. The atrioventricular node was refractory at this interval and the loop was interrupted. Propranolol 2 mg was administered intravenously over two minutes to determine its effectiveness in suppressing the tachyarrhythmia. Approximately seven minutes after the propranolol administration, an atrial premature stimulus with a 280 ms A_1-S_1 interval again initiated an atrial tachycardia at 136/minute. An additional atrial premature stimulus with an A_1-S_1 interval of 280 ms changed the atrial tachycardia to atrial flutter with an atrial rate of 280/minute. The left atrial rhythm continued as atrial flutter at 280/minute, but the right atrial depolarisations became irregular and slower with variable conduction time intervals between the left and right atria (Fig. 1A and B). Fig. 1B shows a recurrent pattern of pro-

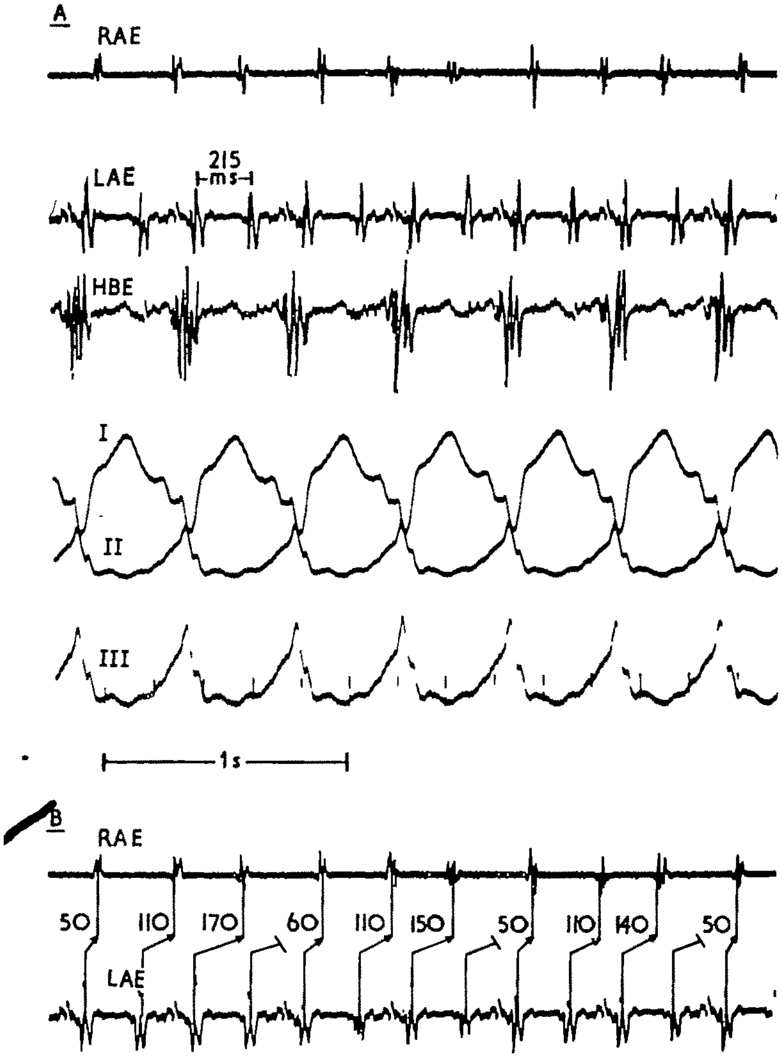

Fig. 1 *(A) Recordings taken during the atrial flutter with left-to-right Wenckebach. The left atrial rate is 280/min (AA interval = 215 ms). The ventricular rate is regular with a constant RR interval of 430 ms. (B) A sketch of the atrial events recorded in Fig. 1A shows the gradual prolongation of the left to right atrial conduction interval (ms) until a left atrial complex is not conducted to the right. RAE, right atrial electrogram; LAE, left atrial electrogram; HBE, His bundle electrogram.*

gressive lengthening of the conduction interval from the left to the right atrium with the eventual loss of a right atrial complex. The interval between the right atrial complexes shortened until a left atrial impulse was not conducted to the right atrium. It is noteworthy that the ventricular rate did not vary during the development of the interatrial block, indicating that the left atrium was activating the ventricles with 2:1 conduction and thus providing further evidence that the accessory pathway is left sided (type A WPW). The 4:3 interatrial block gradually changed into a 2:1 block, resulting in dissimilar atrial rhythms of left atrial flutter at 280/minute and right atrial tachycardia of 140/minute (Fig. 2). The 2:1 interatrial block intermittently reverted to 3:2 or 4:3 interatrial block for brief periods. Several minutes later, the dissimilar rhythms gave way to regular sinus rhythm.

Discussion

This patient illustrates another form of dissimilar atrial rhythms with flutter of one atrium and atrial tachycardia of the other atrium. During the interatrial block the scalar electrocardiogram gave no information about atrial events occurring at the time. This emphasises the importance of recording simultaneous electrograms from each atrium to demonstrate atrial events in patients with atrial arrhythmias.

The biatrial recordings during atrial flutter showed a recurrent pattern of gradual prolongation of the left to right conduction time until a left atrial impulse was not conducted to the right atrium. Concurrently, the right atrial A wave intervals progressively shortened until the dropped right atrial beat (Fig. 1). This pattern meets the criterion

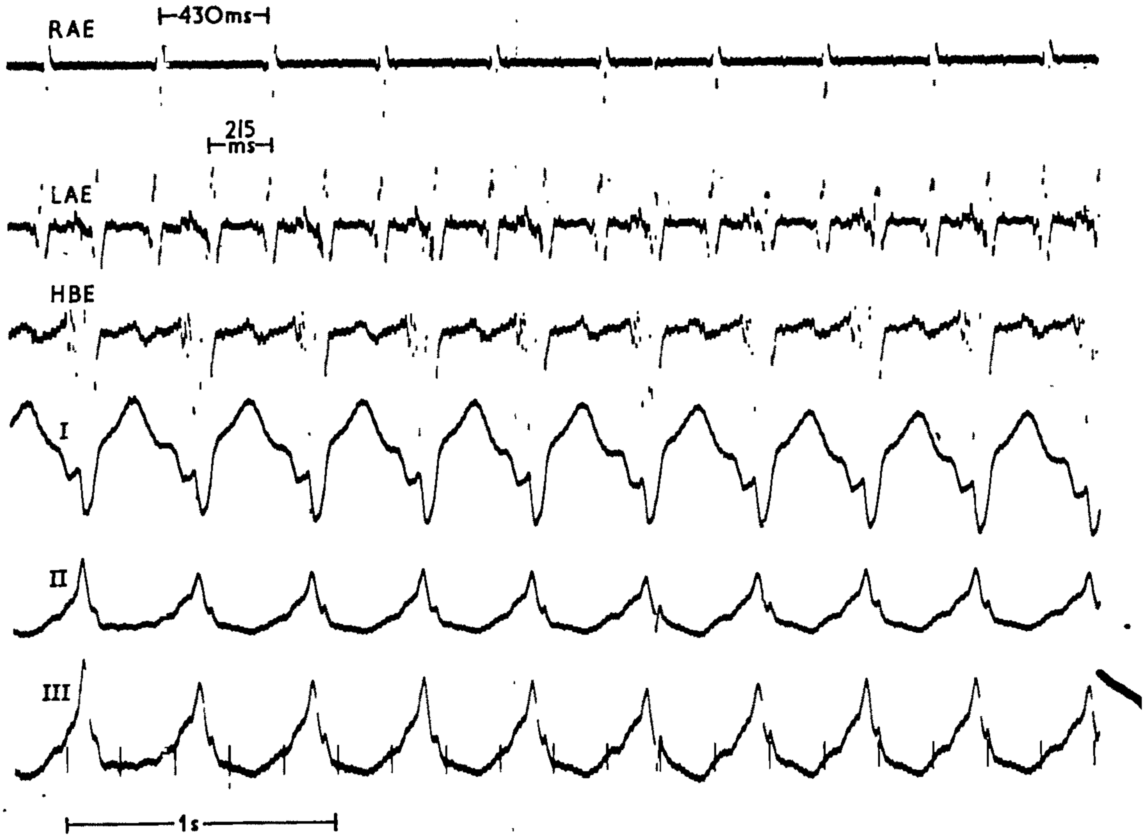

Fig. 2 *The atrial Wenckebach evolves into a 2:1 left-to-right conduction block resulting in right atrial rate of 140/min (AA interval=430 ms) in the presence of a left atrial rate of 280/min (AA interval=215 ms). For abbreviations, see Fig. 1.*

of Wenckebach conduction block. The 4:3 block gradually evolved into a 2:1 block resulting in a right atrial rate of 140/minute during left atrial flutter at a rate of 280/minute. The exact location of the atrial conduction block cannot be determined from the recordings. It is obvious that the block is located somewhere between the right and left atrial recording electrodes. We cannot assume that the atrial septum or Bachman's bundle are the regions of interatrial block since we did not explore the atria with the recording electrodes during the tachyarrhythmia. Though the low right atrial recording was not optimal in quality, most low right atrial deflections occurred in conjunction with the high right atrial deflections, indicating that most of the right atrium displayed the same rhythm.

Lewis *et al.* (1918–1920) produced intra-atrial Wenckebach block in the dog with rapid atrial pacing (369/minute). The atrial Wenckebach phenomenon has also been shown in isolated atrial muscle strips submitted to various physical and pharmacological manoeuvres (Lewis and Drury, 1923; Drury and Andrus, 1924; Drury and Regnier, 1927–1929). Early descriptions of the atrial Wenckebach phenomenon in man were made by Phibbs (1963), Scherf and Cohen (1964), and Schamroth (1967). Narula *et al.* (1971, 1972) documented the occurrence of intra-atrial Wenckebach block in man using intracardiac recordings. They reported patients with abnormal high right to low right atrial conduction times who showed progressive prolongation of this interval during atrial pacing. Intra-atrial Wenckebach block was also documented with intracardiac recordings during atrial pacing (Castellanos *et al.*, 1972). One of their patients also showed progressive prolongation of the right to left atrial conduction interval indicating the presence of right to left interatrial Wenckebach block as well. The baseline prolonged interatrial conduction intervals noted in our patient lengthened with atrial pacing, though right to left atrial Wenckebach block did not develop with pacing rates up to 160/minute. The development of atrial flutter at a rate of 280/minute evoked block in the form of the Wenckebach phenomenon in the conduction pathways from the left to the right atrium. We did not pace the right atrium at rates between 160 and 280/minute to determine if the Wenckebach phenomenon would have occurred from the right to the left atrium.

Atrial conduction block has been shown to be secondary to various anatomical, physiological, and pharmacological factors (Fredericq, 1901; Lewis *et al.*, 1918–1920; Lewis and Drury, 1923; Drury and Andrus, 1924; Drury and Regnier, 1927–1929; Scherf and Siedeck, 1934; Legato *et al.*, 1974; Wu *et al.*, 1975). The patient described here had atrial conduction disease, with prolonged interatrial conduction times during sinus rhythm. The patient was not taking any drugs before the study and thus may have had atrial muscle pathology, as reported by Legato *et al.* (1974). The propranolol administered 7 to 9 minutes before the development of the dissimilar rhythms may have contributed to the atrial conduction disturbance as well as possibly increasing the refractory period (Seides *et al.*, 1974) of the atrial conduction pathways or of most of the right atrium. The right atrial rate was then limited to 140 to 210/minute in the presence of a left atrial rate of 280/minute.

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Infradiaphragmatic total anomalous pulmonary venous connection to portal vein

Diagnostic implications of echocardiography

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A case of total anomalous pulmonary venous connection to the portal vein is described. The diagnosis was suspected clinically, supported by the echocardiogram, and confirmed by cardiac catheterisation, angiocardiography, and contrast echocardiography. An echo-free space lying behind the left atrium initially was thought to represent the common pulmonary vein. However, contrast echocardiography showed that this space was not the anomalous vein but probably an artefact. This paper shows that the origins of intracardiac echoes cannot always be assumed from a simple comparison of echocardiography with angiocardiographic or necropsy findings. In some cases it is necessary to introduce a marker into the echocardiogram which unequivocally originates from, and, therefore, localises, the structure under examination. Contrast echocardiography provides such a marker.

Several echocardiographic features are considered of diagnostic importance in total anomalous pulmonary venous connection. These include right ventricular cavity enlargement and paradoxical septal movement, both suggesting right ventricular volume overload. In addition an echo-free space lying behind the heart has been taken to represent an anomalous common pulmonary vein (Paquet and Gutgesell, 1975).

In this report we present a case of total anomalous pulmonary venous connection to the portal vein in which the diagnosis was suspected on the basis of the clinical picture and the echocardiogram. This was subsequently proven by cardiac catheterisation, including portal vein catheterisation and angiocardiography (Tynan *et al.*, 1974), and the echocardiographic location of the common pulmonary vein was established using contrast echocardiography (Seward *et al.*, 1975).

Clinical information

The infant was born at 36 weeks' gestation (birthweight 2·4 kg). At the age of 14 days he was found to have a systolic murmur at the left sternal edge and was thought to be in cardiac failure. Despite digoxin and diuretics he did not improve and was admitted to this hospital at the age of 24 days.

On examination he was pale and slightly cyanosed with a heart rate of 140 beats a minute. The liver was palpable 3 cm below the right costal margin. On auscultation there was an ejection systolic murmur grade 3/6 at the left sternal edge and wide splitting of the second heart sound with a loud pulmonary component. The chest was clear to auscultation.

Chest x-ray film showed that the heart size was normal and that both lung fields had a faint reticular mottling particularly near the hila. The electrocardiogram showed sinus rhythm, a frontal QRS axis of +170°, and right ventricular hypertrophy.

ECHOCARDIOGRAPHIC FINDINGS

Single probe echocardiography (Fig.) showed a right ventricular end-diastolic dimension of 17 mm and a left ventricular end-diastolic dimension of 6 mm; the aortic root dimension was 8 mm; 4 valves were visualised. Mitral-aortic and septal-aortic continuity and paradoxical septal movement were shown. The left atrial cavity appeared to be of normal size (8 mm). However, behind the posterior aortic wall within the left atrial cavity a constant echo was seen moving parallel to the aorta. This was thought to be an artefact. Posterior to the left atrium there was an echo-free space which was assumed to indicate the presence of a common pulmonary vein.

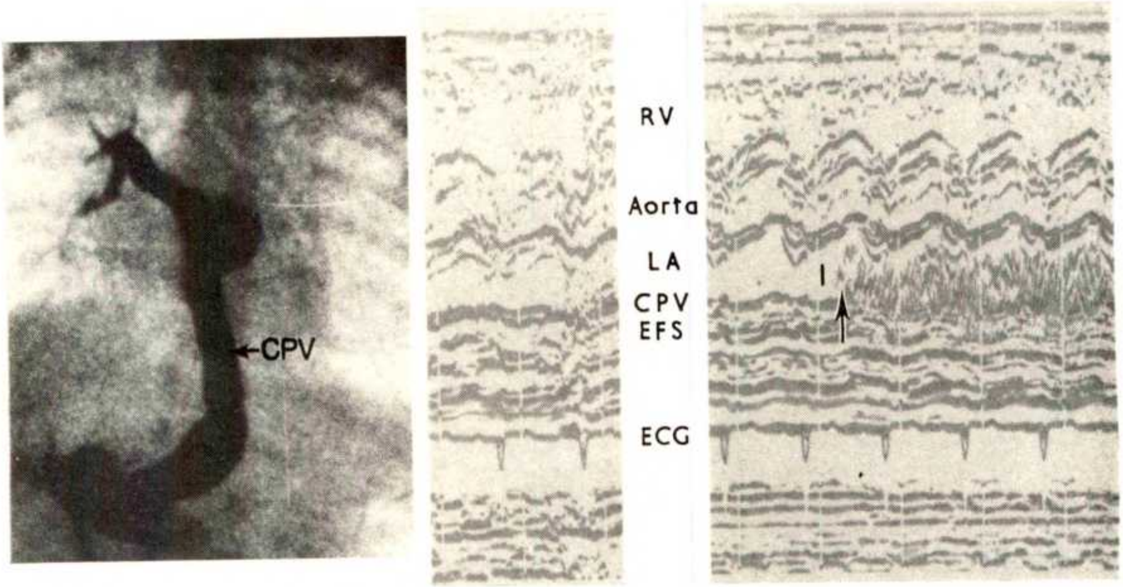

Fig. *Angiogram into the common pulmonary vein (left) with initial echocardiogram (centre) and contrast echocardiogram (right). RV, right ventricle; LA, left atrium; CPV, common pulmonary vein; EFS, echo free space; I, injection of dextrose.*

A presumptive diagnosis of infradiaphragmatic total anomalous pulmonary venous connection was made and the baby underwent cardiac catheterisation.

CARDIAC CATHETERISATION; ANGIOCARDIOGRAPHY AND CONTRAST ECHOCARDIOGRAPHY

Cardiac catheterisation was performed from the right long spahenous vein and the umbilical vein. The findings are summarised in the Table. The common pulmonary vein was entered from the umbilical vein using a Muller guide system. Before angiography a contrast echocardiogram was performed by injecting 2 ml 5 per cent dextrose into the common pulmonary vein while the echo probe was positioned to visualise the aorta, the left atrium, and the previously noted echo-free space. The injection of dextrose opacified the lumen of the common pulmonary vein showing that it occupied most of what had previously been thought to be the left atrium (Fig.) and that the true dimension of the left atrium was only 3 mm. The echo free space lying posteriorly to the heart did not appear to be part of the pulmonary venous system. Cineangiography into the common pulmonary vein (Fig.) established the diagnosis and showed that the contrast echocardiogram had been performed in the common pulmonary vein.

Discussion

Echocardiography is of considerable diagnostic value in infants with congenital heart disease (Godman *et al.*, 1974). There are, however, limitations to the technique which are related to the variability in the anatomy and haemodynamics of the malformations encountered in the newborn period. Thus, a normal echocardiogram has been recorded in a case of total anomalous pulmonary

Table

	Pressures (mmHg)	*Oxygen saturation (%)*
Superior vena cava		23
Inferior vena cava		
suprahepatic		65
infrahepatic		34
Right atrium	mean = 7	85
Right ventricle	70/9	86
Main pulmonary artery	60/25	78
Left atrium	mean = 7	86
Left ventricle	50/6	84
Descending aorta	47/25	93
Right pulmonary vein	20/16	
Left pulmonary vein	20/16	
Common pulmonary vein	20/16	97
Portal vein	18/14	
Umbilical vein	6/0	93

venous connection to the portal vein where the confluence of the pulmonary veins was close to the diaphragm (Hagler, 1976). Because of this variability, it is essential, in the present state of our knowledge, to validate wherever possible the origin of echoes related to the heart. This report shows that contrast echocardiography performed at catheterisation has a valuable role to play in this process.

An echo-free space bounded by thick continuous echoes lying posteriorly to the left atrium is a common finding in infants and small children. In this case the clinical profile suggested that the diagnosis was obstructed total anomalous pulmonary venous connection. We, therefore, misinterpreted the significance of these echoes and took the space to represent the common pulmonary vein. However, contrast echocardiography showed that these echoes did not originate from the common pulmonary vein. Their origin remains speculative. They may represent part of the descending aorta or left pulmonary artery or they may be artefacts. In retrospect a normal-sized left atrial cavity is an unlikely finding in infradiaphragmatic total anomalous pulmonary venous connection (Glaser *et al.*, 1972) and contrast echocardiograms showed that the true left atrial dimension in this case was very small.

The clinical and echocardiographic appearances may be similar in cortriatriatum and at present the differentiation of this condition from obstructed total anomalous pulmonary venous connection may not be possible without cardiac catheterisation. If either of these conditions are suspected clinically the abnormal echoes arising from the anterior wall of the common pulmonary vein or the septum separating the triatrial chamber from the left atrium should be sought within the apparent left atrial chamber and not necessarily posterior to it.

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Massive digoxin ingestion
Report of a case and review of currently available therapies

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Recent reports of treatment of massive digoxin overdosage have emphasised the success of medical therapy. This report describes a fatal outcome to this problem despite aggressive medical management, including pervenous cardiac pacing and draws attention to deficiencies in current treatment of a serious problem.

Digoxin toxicity is not uncommon (Beller *et al.*, 1971; Boston Collaborative Drug Surveillance Program, 1972) and depends for successful treatment on its prompt recognition and withdrawal of glycoside therapy. This simple approach usually suffices and may be improved by routine monitoring of serum digoxin levels to detect occult toxicity.

Massive digoxin overdose is uncommon but much more dangerous: recent reports of successful management tend to obscure the high mortality rate, which may reach 20 per cent (Smith, 1973).

Case report

A 71-year-old man was admitted to the coronary care unit of the Royal Infirmary, Glasgow, some 14 hours after suicidal ingestion of 83 'Lanoxin' (Burroughs Wellcome) tablets of 0·25 mg strength. The number ingested was confirmed from the prescription date on the bottle.

The patient had been taking 0·25 mg digoxin per day together with a thiazide diuretic and potassium supplement for mild cardiac failure. He suffered from angina and prostatism and recently had been depressed.

On admission, the patient was semicomatose, hypotensive ([illegible]0/60 mmHg), and vomiting repeatedly. He had no diarrhoea.

INVESTIGATIONS

An initial 12 lead electrocardiogram showed widespread ST depression and lead V6 detected a self-terminating run of ventricular tachycardia. Plasma electrolytes on admission were: Na 137, K 3·1, Cl 91, urea 7 mmol/l. Arterial blood gases were $\mathrm{Po_2}$ 58 per cent and $\mathrm{Pco_2}$ 31 per cent with *p*H 7·31. Magnesium and calcium levels were normal.

Haematology

Haemoglobin 18 g/dl; PCV 58 per cent, WBC $6{\cdot}4\times10^9$/l. Chest *x*-ray examination indicated a normal cardiac contour and possible pulmonary congestion.

Cardiac enzymes (on admission and 6 hours later) were subsequently reported to be normal.

Blood was drawn for digoxin radio-immunoassay. The level on admission was subsequently reported as 36·8 ng/ml (serum), and 45 minutes before death, the level was 56 ng/ml.

Six hours after admission, electrolyte parameters were Na 130, K 4·4, Cl 93, urea 7·5 mmol/l. Arterial blood *p*H was 7·31, $\mathrm{Po_2}$ 65 and $\mathrm{Pco_2}$ was 41 (on 6 litres oxygen/minute).

PROGRESS AND MANAGEMENT

Cardiac rhythm was continuously monitored on a Hewlett-Packard video monitor with push-button recall and recording capacity.

Intravenous fluid replacement was started with normal saline and dextrose solutions with potassium supplements.

Vomiting ceased after intramuscular prochlorperazine.

In view of the hypotension, bladder catheterisation was performed to facilitate adequate monitoring of renal function. Urine output was initially low (urine osmolality 650 mosmol/kg), improved with fluid replenishment and intravenous mannitol, but later declined again.

The patient's condition deteriorated and atropine-resistant bradyarrhythmia became more frequent. Under lignocaine cover (100 mg bolus and an infusion of 2 mg/min), a pacing catheter was passed from an antecubital vein to a pacing position on the floor of the right ventricle (threshold 0·4 volt).

Passage through the tricuspid valve induced ventricular fibrillation which was converted with three DC shocks of 50, 100, and, finally, 200 joules to a nodal bradycardia that permitted demand pacing at 100 beats/minute initially, subsequently reduced to a rate of 70/minute.

TREATMENT OF SUBSEQUENT RHYTHM DISORDERS

Sinus and nodal bradycardias were unresponsive to atropine (1·2 mg i.v.), and required pervenous pacing to maintain adequate organ haemoperfusion.

Runs of ventricular tachycardia were frequently self-terminating but where prolonged were treated with lignocaine bolus therapy (50, 100 mg i.v.). The prophylactic lignocaine infusion (2 mg/min) was maintained for 2 hours with no apparent reduction in the frequency of tachyarrhythmia and, therefore, was discontinued. To avoid lignocaine toxicity, boluses of practolol, procainamide and phenytoin were used in rotation to treat tachyarrhythmias causing haemodynamic deterioration. Procainamide was used sparingly in view of the patient's persistent hypotension.

Supraventricular tachycardias were treated with boluses of practolol and on two occasions, where they proved resistant to practolol, with procainamide boluses.

Some runs of supraventricular tachycardia changed to ventricular tachycardia and were aborted with lignocaine or procainamide boluses.

The practolol infusion (20 mg per 6 hours) was instituted to block digoxin-induced sympathetic stimulation and to raise the threshold for digoxin-induced ventricular fibrillation (Tse and Han, 1974).

Verapamil (10 mg i.v.) was given on two occasions: firstly, for a supraventricular tachycardia → ventricular tachycardia arrhythmia on the basis that this sequence might indicate a re-entry phenomenon—the tachycardia persisted until procainamide was given—and, secondly, for a run of atrial tachycardia with varying block—this arrhythmia changed to a rapid supraventricular tachycardia but then recurred.

A prolonged run of 2:1 atrial flutter was unresponsive to intravenous disopyramide, but converted with a procainamide/practolol bolus combination to a nodal bradycardia, permitting re-establishment of pacing rhythm.

TERMINAL EVENTS

By seven hours after admission, the ventricular complexes (both paced and unpaced) showed widening of the left bundle-branch block variety, the pulse volume was weak and urine output had fallen to 8 ml/hr.

Cardiac screening showed no change in pacemaker tip position but the pacing threshold had risen to 3·0 volts.

By this time, the patient had received, in divided doses, 820 mg lignocaine, 550 mg procainamide, 45 mg proctolol, 200 mg phenytoin, 20 mg verapamil, and 100 mg disopyramide.

Over the next two hours, the patient paced satisfactorily with no major rhythm upsets. The only therapy was a practolol infusion of 20 mg/6 hourly.

Nine hours after admission, an asystolic cardiac arrest occurred. External cardiac massage was initiated with no response. Cardiac pacing was unsuccessful despite re-manipulation and raising the pacing stimulus to 6 volts. Atrial pacing, similarly, was ineffectual.

Intravenous isoprenaline, 0·5 mg, induced coarse ventricular fibrillation but cardioversion at 30 joules produced a slow idioventricular rhythm that responded for a few beats to demand pacing, then reverted to ventricular fibrillation. Attempts to control the ventricular fibrillation by defibrillation, pacing, and phenytoin and procainamide boluses were unsuccessful and resuscitation was eventually abandoned.

Discussion

With the plethora of potentially useful (and hazardous) drugs currently available to treat massive digoxin overdosage, it is important to adopt a rational approach to this serious condition.

Firstly, it should be emphasised that digoxin-induced arrhythmias change frequently and spontaneously. Bigeminy does not necessarily portend ventricular tachycardia and the latter disorder may remit spontaneously. It follows that arrhythmias only require treatment if they cause haemodynamic deterioration. Attempts to use lignocaine or prophylatic practolol may be of little value and may in fact reduce the choice of therapy for the life-threatening arrhythmias.

Secondly, it is vital to reduce absorption, facilitate elimination of the drug and to deal with factors that potentiate the toxicity of digoxin. Gastric lavage should be performed when patients present shortly after ingestion or where vomiting has not occurred. Purging, with close monitoring of plasma electrolytes, should also be considered, and might well have been beneficial in this case, in the light of the rise in serum digoxin levels after admission.

Maintenance of a good urinary output is mandatory as this is the major excretory route for digoxin. Mannitol is probably the safest diuretic, as electrolyte imbalance is least likely with osmotic diuretics. Maintenance and frequent monitoring of plasma electrolytes and *p*H are important as massive digoxin ingestion may produce hyperkalaemia caused by generalised cellular loss of potassium from blockage of the membrane sodium-potassium-pump, with subsequent cardiac arrest (Citrin *et al.*, 1972; Bismuth *et al.*, 1973). Induction of hyperkalaemia has been proposed as a therapeutic measure in digoxin overdosage as raised plasma potassium levels antagonise glycoside uptake at the sodium-potassium-pump site (Porter, 1974). This approach, however, may exacerbate bradycardia as potassium, while opposing digoxin-induced delay through the AV node, slows cardiac conduction by delaying transmission above and below the node (Dreifus *et al.*, 1974; Cohen *et al.*, 1975). Moreover, the beneficial effect of potassium is much reduced if given after glycoside fixation to cardiac tissue. This particular patient was hypokalaemic because of the central emetic effect of digoxin, and replenishment was undertaken cautiously as intermittent AV block was present.

Hypercalcaemia and hypomagnesaemia similarly potentiate digoxin toxicity (Nola *et al.*, 1970; Lee and Klaus, 1971; Seller, 1971 Beller *et al.*, 1973). Hypoxia was treated by controlled oxygen therapy (Harrison *et al.*, 1968; Beller and Smith, 1972; Beller *et al.*, 1973).

The *p*H was maintained by loss of gastric vomitus: acidosis appears to exert its potentiating effect through alterations in potassium (Bliss *et al.*, 1963).

Thirdly, attention is directed towards life-threatening arrhythmias. Sinus and nodal bradycardias may result from digoxin-induced vagal stimulation and will respond to atropine particularly shortly after digoxin ingestion. Resistance tends to appear (as here) probably because of binding of glycoside to cardiac tissue and direct effects of digoxin on sinus and AV nodal function. In these circumstances cardiac pacing is required.

Ventricular tachyarrhythmias are probably best treated in the first instance by lignocaine therapy as this drug is rapidly effective and, equally important, of short-lived effect. Hypotension is rarely a problem. A lignocaine bolus probably distributes itself into three compartments in man, with half-lives of 9, 40, and 120 minutes (Jewitt, 1975); the first compartment is of primary importance for antiarrhythmic action, but with repeated boluses other compartments may become saturated and toxic levels may be attained with the production of convulsions. Destruction is by hepatic microsomal enzymes.

A procainamide bolus may convert ventricular tachycardia but its use is limited by its slow rate of detoxication (10 to 15% of the bolus per hour) and by its tendency to cause hypotension. It does, however, have some anticholinergic activity and, unlike lignocaine, is effective in supraventricular tachycardia. Procainamide-induced asystole is relatively common in the presence of digoxin, and pacing may be life-saving.

Phenytoin is of similar efficacy to procainamide and has been recommended in digoxin overdosage on the grounds that it does not depress AV conduction (Mason *et al.*, 1971; Rumack *et al.*, 1974). However, the authors have observed that the combination of phenytoin and practolol induced complete heart block on two occasions in the same patient (with recurrent ventricular tachycardia secondary to ischaemic heart disease), and it may be that this potential benefit of phenytoin depends on the age and integrity of the conduction system. With a pervenous pacemaker *in situ,* this advantage is largely annulled.

Beta-adrenoreceptor blockade will abort digoxin-induced supraventricular tachycardia and, possibly, ventricular tachycardia (as apparently occurred here). There is evidence that digoxin poisoning can cause general sympathetic stimulation, both central and peripheral, and sympathetic stimulation lowers the threshold for digoxin-induced ventricular fibrillation (Tse and Han, 1974). On the basis of this evidence, practolol was used in bolus form to treat arrhythmia and as an infusion to counteract catecholamine discharge. Phenytoin is also said to oppose the central sympathetic effects of cardiac glycosides (Evans and Gillis, 1975).

The value of other antiarrhythmic drugs in digoxin poisoning is supported by experimental studies of their potential in opposing glycoside-induced ventricular fibrillation (Jewitt, 1975), but there is little experience of their efficacy in human overdosage. Verapamil, for example, was ineffective in this patient, as was disopyramide.

The ineffectiveness of verapamil merits further comment as this drug has been recommended in the treatment of atrial tachycardia with block on the basis that this rhythm is due to AV nodal re-entry (Storstein and Landmark, 1975). AV nodal action potentials are largely the result of the slow inward calcium current (which is not completely calcium-specific and may include a sodium component)

(Paes de Carvalho *et al.*, 1969), and verapamil antagonises the calcium influx through this channel. Theoretically, therefore, this drug should offer distinct advantages in the treatment of atrial tachycardia (and this has been shown to be so by Storstein and Landmark, 1975; Spurrell *et al.*, 1974) and also of digoxin intoxication as digoxin appears to augment calcium influx by increasing intracellular sodium. The lack of effect in this patient may indicate that the toxic effects of digoxin were too far advanced for verapamil at the chosen therapeutic dose to reverse the rhythm abnormalities.

Cardioversion should be a last resort: digoxin excess lowers the size of shock required and tends to produce intractable or recurrent tachyarrhythmias (Ten Eick *et al.*, 1967; Peleška, 1963; Lown *et al.*, 1965).

The inexorable decline in response to pacing is probably a measure of increasing glycoside fixation to cardiac tissue, as is the resistance of bradycardias to atropine.

Digoxin appears to exert its effects on cardiac tissue by blocking the membrane-located sodium-potassium pump: the consequent rise in intracellular sodium accelerates transfer of calcium into cells in exchange for sodium; the rise in internal calcium augments myocardial contractility by activating troponin.

Toxicity is primarily a pharmacological extension of this action of digoxin with ionic imbalance predisposing to ectopic activity re-entry rhythms, and conduction delay or enhancement. At high glycoside levels, calcium accumulates at cell nexuses producing electrical uncoupling and failure of impulse transmission (Weingart, 1975). This was the probable terminal sequence in this patient. The plasma digoxin levels recorded here are possibly the highest recorded in a human being.

Currently, the major problem in reversing digoxin toxicity is the lack of a generally available method of removing glycoside from the bloodstream. Haemodialysis and charcoal perfusion are valueless.

Recently, Smith *et al.* (1976) have shown the effectiveness and safety of an infusion of Fab fragments purified from digoxin antibodies in leaching out digoxin from tissues in animals and in a human patient; the fragments attach to glycoside and are sufficiently small to permit glomerular excretion. This promises to be a major breakthrough in the treatment of a difficult problem.

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Requests for reprints to Dr. W. F. Bremner, University Department of Medical Cardiology, Royal Infirmary, Glasgow G4 0SF.

Obituary

British Heart Journal, 1977, **39**, 693-695

Graham William Hayward

Graham Hayward was born in Cardiff and died in London on 26 November 1976 at the age of 65, six months after his retirement as senior physician to St. Bartholomew's Hospital and The National Heart Hospital.

He was educated at Cardiff High School and entered The Welsh National School of Medicine, then under the aegis of the University College, Cardiff, in October 1928. He gained the BSc in June 1931 with distinctions in anatomy, physiology, and pharmacology and received the Alfred Hughes Memorial Medal in anatomy and the David Hepburn Medal for the highest aggregate of marks in the annual degree examinations in human anatomy, anthropology, embryology, and histology. Even at this stage it was clear to his friends that he was a man of academic brilliance but he also distinguished himself as a sportsman and was a tower of strength as a member of The Cardiff Medical Students Rugby Club. Hayward then went to St. Bartholomew's Medical College and carried on as he had started by winning the Kirke's Scholarship in comparative anatomy, the gold medal in clinical medicine, the Brackenbury prize in medicine and the Willett medal in operative surgery. These were the major prizes at his Medical School. During this time he was a heavyweight boxer of repute and represented the University of London, but obviously was never knocked out or concussed. He was also an outstanding lock forward combining his physique with intelligence and knowledge of the basic principles of the rugby game. The qualifications of MRCS, LRCP posed no problems in January 1935 and in May of the same year he sat his MB, BS in five subjects—medicine, surgery, pathology, midwifery and gynaecology, and forensic medicine and hygiene and obtained distinctions in all—a very rare achievement and naturally was awarded the University Gold Medal. Surely, this is a remarkable undergraduate record and probably quite unique. Two years later he acquired the MD (Lond) and MRCP and was elected FRCP in 1946.

After being Professor L. J. Witts' house physician Hayward was appointed resident medical officer at the National Hospital for Diseases of the Heart and remained there for one year and consequently he became interested in cardiology. In 1937 he was awarded a Rockefeller Foundation Fellowship at The Penna Hospital, Philadelphia, and during that time his main research activity included metabolic disorders and the action of insulin. Early in 1939 he was appointed demonstrator in physiology and pharmacology at St. Bartholomew's Medical College and did much research into pulmonary congestion and oedema. He was given the Mackenzie McKinnon research fellowship of the Royal College of Physicians to continue this work but the war intervened. In May 1940 he was appointed as chief assistant to the medical professorial unit under the directorship of Professor R. V. Christie but soon after this he enlisted in the army and served in the Middle East and Italy as OC Medical Division of the 3rd New Zealand Hospital. Amoebiasis attracted his attention during his overseas tour, and he lost no time in evaluating the effect of emetine upon the heart. Immediately after his demobilisation in 1946 he was appointed as assistant physician at St. Bartholomew's Hospital and in 1947 was appointed to the staff at The National Heart Hospital. He was Dean of the Institute of Cardiology of the University of London from 1948 until 1961 and gave the St. Cyres Lecture in 1954. Hayward worked with Christie as assistant director on the professorial unit at St. Bartholomew's and also with Geoffrey Bourne. After Bourne's retirement he became physician-in-charge of the Department of Cardiology and much of its subsequent prestige was due to his dominant and conscientious presence.

His unequalled achievements in academic medicine he matched with the skill he acquired as a practising physician. In spite of acknowledged distinction in both fields, his modesty remained proverbial. When asked the reason for his internationally recognised expertise in the diagnosis and treatment of infective endocarditis he characteristically answered that all the credit was due to his distinguished colleagues in the Department of Bacteriology at St. Bartholomew's.

Hayward gave the Croonian Lecture on 'Infective endocarditis—a changing disease'—at the Royal College of Physicians in 1972.

Always affable and courteous, he easily forged friendships which he kept in constant repair, and thus a friend was never lost. He wore an indwelling smile with a ruddy complexion but when he lowered his face to look over his familiar half-moon spectacles his gaze was both penetrating and discerning but always with a twinkle.

He added dignity and lustre to his profession and he cared not to sparkle through indulging in unorthodoxy in either the investigation of a patient's illness, nor through excessive zeal in its treatment. In Hayward's hands the management of a patient could never be faulted, while if he considered drug treatment invalid he could dispense encouragement in telling words so that the patient felt better after seeing him. Let two patients testify to this. The one said, 'I left his consulting room with new strength to bear my illness', and the other 'I felt he understood me and my problems and I trusted him implicitly, he was a wonderful doctor.' In many homes he will be remembered for the timely application of his skill, sound judgement, human understanding, and sympathy. He was indeed a doctor of men as well as of their diseases—the complete general physician. Great in stature, great in thought, deep in voice, and endowed with so much common sense, patients and colleagues were quick to appreciate that they were in the presence of a great man who commanded instant respect. He just radiated confidence and security. His integrity and honesty were obvious to all and his humility and shyness confirmed the greatness of the man. Graham Hayward never sought any power and according to him there were always better men than he and more suitable to a particular distinction, honour, or appointment.

At St. Bartholomew's and the National Heart Hospitals he had frequently to chair meetings to discuss diverse matters, when he would not impose his will nor oppose compromise provided it did not offend tested principles. His sane and calculated opinion was always sought in general hospital affairs to the benefit of his colleagues and the administrators who all appreciated his scrupulous fairness and critical thinking. For some time he was Adviser in Cardiology to the Ministry of Health and they certainly needed a man of this calibre to guide them. With such vast clinical experience in general medicine and cardiology in particular, he was a superb and popular undergraduate and postgraduate teacher and was able to graft the practitioner's art onto the main trunk of the fundamental sciences to the lasting benefit of his pupils. Hayward recognised that for the good doctor the clinical method of history taking and detailed methodical examination of his patient still took pride of place and that without such a clinical method modern medicine would become a chaos of activities and invasive techniques.

Between 1952 and 1958 he was an examiner in medicine at the Universities of London, Cambridge 1958, Khartoum 1956, and in 1959–60 at the University College of The West Indies.

Graham Hayward was a very active member of the British Cardiac Society for 28 years and was a member of its Council from 1953 to 1957 and from 1963 to 1967. He was Chairman of the Autumn Meeting in London in 1966. At its meetings he was never prone to enter into the discussions even when his assistants had given a paper. He preferred to listen attentively, assess the merit or otherwise of the various contributions and if pressed would give his opinion in a more convivial atmosphere than the lecture theatre. At the end of a day of numerous papers he was able to distinguish the important contributions that had been made and would give solace to those of his friends who had only understood a few. To listen to Graham Hayward on such occasions—and he had to be prompted and cajoled to give his opinion—was a revelation of his critical and clear thinking, with always a bias towards patient care because this was his main occupation in medicine. He contributed many publications on cardiovascular subjects, mainly in the *British Heart*

Journal, The Lancet, The British Medical Journal, and the *Proceedings of the Royal Society of Medicine.* All were of the highest standard, all withstood critical appraisal with credit, and all conveyed a clear message.

His untimely death, so early in retirement, robbed him of his entitlement to enjoy more time at gardening, a recreation he had planned to follow, but it was not to be. We pay tribute to a great physician and cardiologist and a great man who will be sorely and sadly missed by his patients, colleagues, students, and friends.

As Graham Hayward faced each full and arduous day's work and returned from it in the late evening, he too found the same healing comfort and help he had dispensed to others during the day from his loving wife Mary Anna, to whom along with their three children we extend our warm sympathy. May they be given grace to bear cheerfully their great and irreparable loss. BYRON EVANS

Correspondence

British Heart Journal, 1977, **39**, 696–697

Sudden death of 7th Duke of Marlborough

Sir,

It seems to be widely believed that the nineteenth century physicians were, rather surprisingly, unfamiliar with coronary artery disease. In this context, your readers may be interested in a letter which recently came to light, in which Sir William Gull writes to William T. Gairdner, then Professor of Medicine in Glasgow, to give him the facts relating to the sudden death of the 61-year-old Duke of Marlborough.

July 14, 1883.

71, Brook Street,
Grosvenor Square, W.

Dear Dr. Gairdner,

The circumstances under which the Duke of Marlborough died were rare, though not peculiar. During life, the heart was from time to time examined, but there was nothing that could be noted abnormal either in the rhythm or sounds.

There had never been any symptoms of angina.

Postmortem. The coronary arteries of the heart were found atheromatous and calcareous, with obliteration of some branches. Cardiac muscle fibroid in corresponding points.

These facts I believe are the main ones of the case, so far as the mode of death went;—which must have been quite sudden.

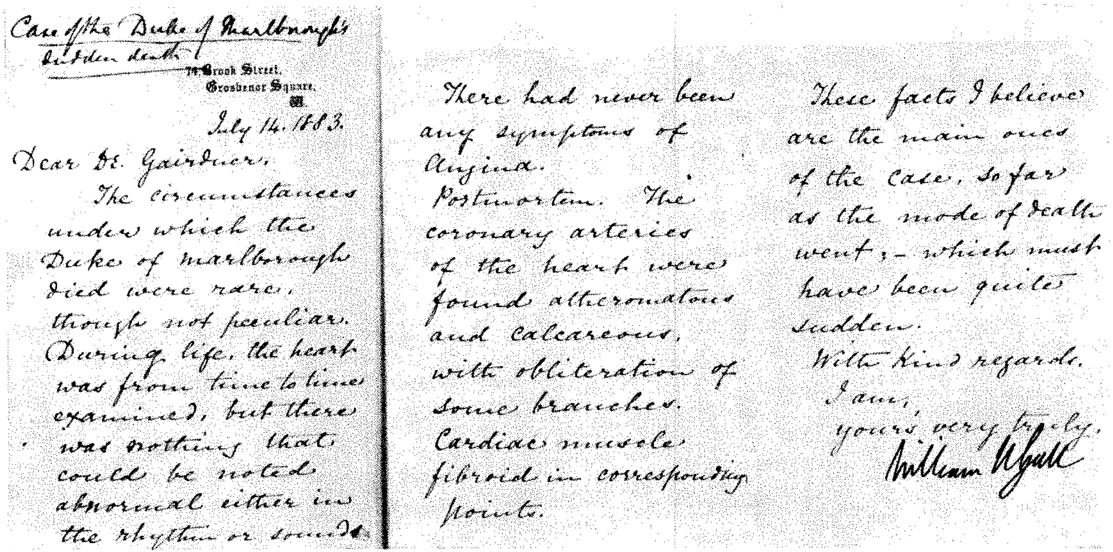
With kind regards, I am,

Yours very truly,
William W. Gull

An additional note headed 'Information from a daughter', and dated July 8, 1883, states:

'Neither Gull nor Acland had the least suspicon of heart disease. Had no symptoms of it—was strong on the moors last season. Talked with his son Randolph on the Egyptian political affair till 11·15.

'Had undressed, wound up his watch, lit his wife's nightlight in next room, shut the door and was found on the floor in his dressing gown.



Case of the Duke of Marlborough's sudden death

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Grosvenor Square,
W.

July 14. 1883.

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With kind regards, I am,
yours very truly,
William W Gull

'Ossification of the valves found after death.'

Gairdner was, like Gull, a cardiologist and the letter implies that cardiac infarction was in fact well accepted, at least among cardiologists of the day, as a cause of sudden death, which might or might not be preceded by anginal symptoms.

The reference to Egyptian affairs may interest students of the history of the times, who will recall that in the preceding year (1882) British troops had landed in Egypt and, after the battle of Tel-el-Kebir, had restored the Khedive who had been deposed in a coup d'état by Arabi Pasha. Lord Randolph Churchill (Winston Churchill's father) had become the leader of a group in the House of Commons which fiercely opposed the Gladstone government's Egyptian policy and supported the Arabists. One of Arabi's officers was summarily executed in defiance of an assurance by the Government to examine his case, and it was no doubt this event which Lord Randolph was discussing with his father so shortly before the latter's death.

Douglas Gairdner,
17 Rutherford Road,
Cambridge CB2 2HH

Announcement

British Heart Journal, 1977, **39**, 698–699

European Society of Cardiology Bulletin

At the time of the Congress of the European Society of Cardiology at Amsterdam, there were several discussions concerning how the European Society of Cardiology could provide better and regular information on its activities to all its members. There was general agreement that the simplest way of effecting this was by publishing notices in the various European journals of cardiology or internal medicine.

The Board of the European Society of Cardiology is, therefore, grateful to the editors and publishers of journals who have kindly agreed to help. It is hoped that this will not only provide a means of diffusing information from the Board to the members, but will also encourage individual members to communicate with the Board on questions of general interest.

According to the Statutes of the European Society of Cardiology a new Board was elected by the General Assembly for the period from 1976–1980. The election took place on 25 June 1976, during the Congress of the European Society of Cardiology at Amsterdam:

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Telephone: 343.92.57

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Budejovicka 800,
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The Statutes of the ESC were amended in several points and accepted by the General Assembly. In accordance with Article 8 of the 'Standing Orders' the Board has selected 15 working groups. The functions of the working groups are outlined in Article 8 as follows:—

(1) To promote and organise research in the subject.

(2) To gather together and exchange information.

(3) To contribute to the organisation and preparation of congresses, scientific meetings, and symposia.

The topics and chairmen of the working groups will be given in the next bulletin.

The following is a list of meetings which will be sponsored by the ESC during 1977. Many of these meetings are in association with meetings of the working groups. The Board believes that it is desirable for as many meetings as possible to be 'open', at least to local members. On the other hand, it appreciates the difficulties involved in organising such meetings and realises that 'open' meetings might not always be practicable, especially when they may be regarded as the work of an 'expert' committee.

June 23-24, Rotterdam. 'Echocardiography'

Open

Correspondence address: Symposium on Echocardiography, Thoraxcentrum, Erasmus University, P.O. Box 1738, Rotterdam, The Netherlands

September 4–6, Utrecht. 4th Workshop on Contractile Behaviour of the Heart. 'Relaxation and Diastole'

Open—limited to 200 participants

Secretary: Prof. F. L. Meijler, Department of Cardiology, University Hospital, Catharijnesingel 101, Utrecht, The Netherlands

September 23–24, Lyon. 'Aortic valve disease in adults'

Open to local cardiologists

Secretary: Prof. J. Delaye, Hôpital Cardio-Vasculaire et Pneumologique, B.P. Lyon-Montchat, 69394 Lyon 3e, France

September 29–October 1, Rotterdam. '5th Annual Conference on Computers in Cardiology'

Open

Secretary: Prof. P. G. Hugenholtz, Medische Faculteit Rotterdam, Thoraxcentrum, Postbus 1738, Rotterdam, The Netherlands

October 5–8, Barcelona. 'International symposium on the diagnosis and treatment of cardiac arrhythmias'

Open

Secretaries: Dr. A. Bayés de Luna and Dr. L. Sanchéz-Harguindey, OTAC, S.A. Organización y Servicio de Congresos, Apartado de Correos 22.055, Barcelona, Spain

December 2–3, Paris. 'Isotopes'

Open

Secretary: Prof. M. Degeorges, Hôpital Cochin, 27 rue du Faubourg Saint Jacques, 75014 Paris, France

Notices

British Heart Journal, 1977, 39, 700

International Cardiopulmonary Symposium, Bombay, 13-15 November 1977

An International Cardiopulmonary Symposium will be held at Hotel President (India), Bombay, from 13 to 15 November 1977. The Symposium is being sponsored by the Western India Chapter, International Academy of Chest Physicians and Surgeons (affiliated with the American College of Chest Physicians), and Association of Physicians of India and its Bombay Branch, and Indian Association for Chest Diseases. The Symposium in which many international authorities are participating will deal with advances in cardiopulmonary medicine and surgery. For further information, write to Dr. M. Paul Anand, Secretary General, International Cardiopulmonary Symposium, 4 Narendra Bhuvan, Bhulabhai Desai Road, Bombay 400 026.

International Union of Angiology

First Announcement—XIth International Congress of Angiology, Prague, Czechoslovakia, 2–8 July 1978. Adaptability of the vascular wall; physiopathology, diagnosis, and therapy of vascular diseases.

Local organising committee:

President: Z. Reiniš, Prague, Laboratory of Angiology.

General Secretary: J. Pokorný, Prague, IVth Medical Clinic.

Scientific Secretary: J. Linhart, Prague, IKEM.

We announce with regret the death of
the associate editor, Dr. Dennis Deuchar.
An obituary will be appearing in a future issue.

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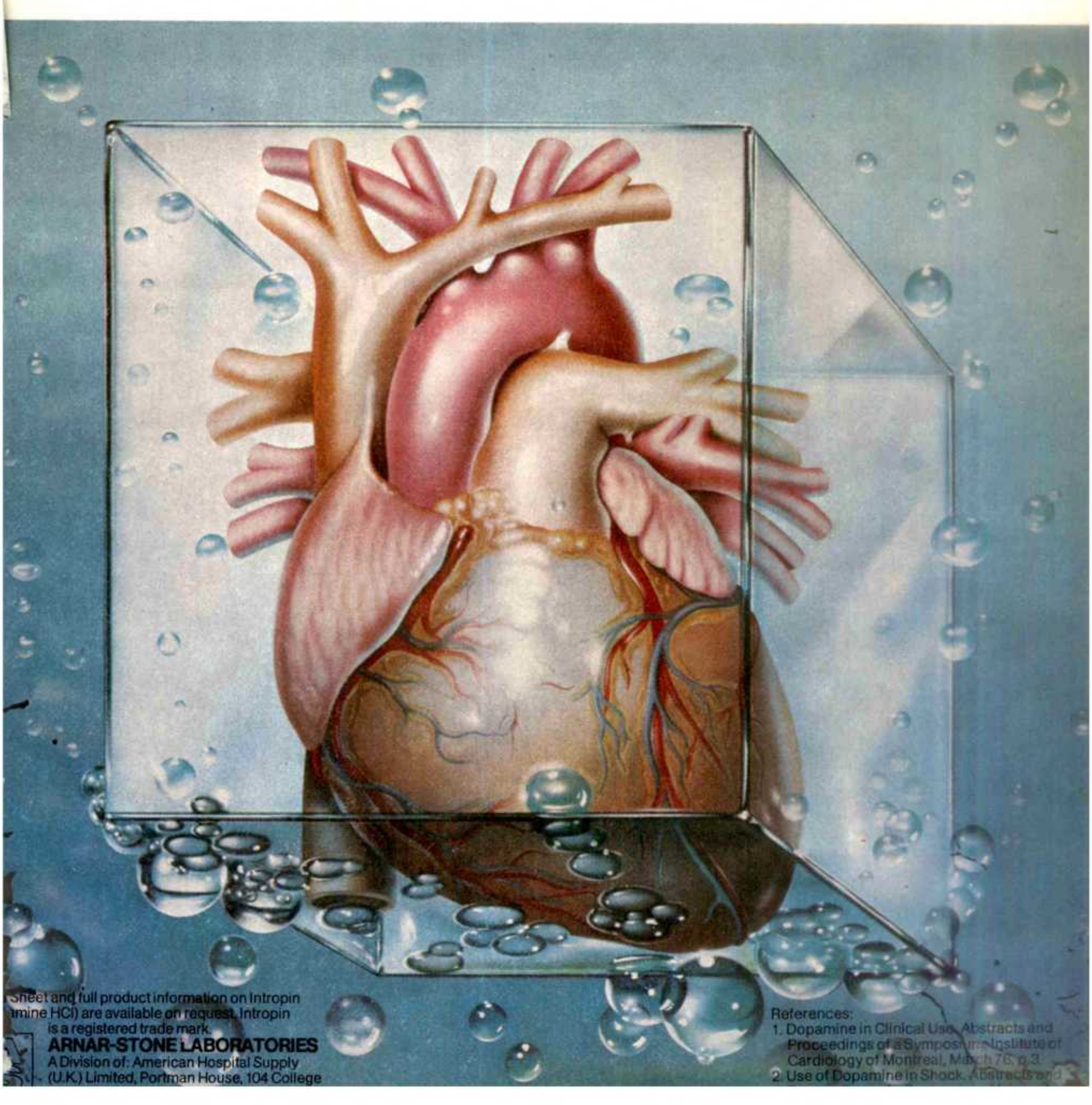

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References:
1. Dopamine in Clinical Use. Abstracts and Proceedings of a Symposium, Institute of Cardiology of Montreal, March 76, p 3.
2. Use of Dopamine in Shock. Abstracts and

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This book will enable all those interested in cardiology to keep abreast of contemporary views on the diagnosis, assessment and management of this common and disabling condition.

Contents and Contributors
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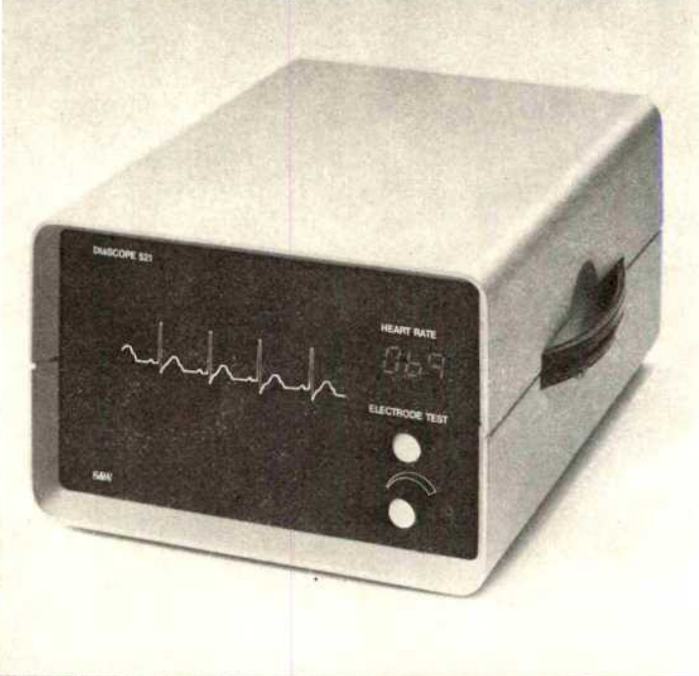

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“Burinex was extremely well tolerated.”[12]

“Bumetanide was well tolerated by patients.”[1]

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“It is known from short-term studies that 1 mg. of bumetanide increases the excretion of potassium by 10-15mmol daily (Asbury et al, 1972; Olesen et al, 1973; Davies et al, 1974). Two tablets of the combined preparation Burinex K contain 1 mg. of bumetanide and 16mmol of potassium.”[8]

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1. Postgrad. Med. J., 51, 10, (1975)
2. Danish Med. Bull., 21, 63, (1974)
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14. J. Int. Med. Res., 4, 37-41 (1976)

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